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Archives of Internal Medicine

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LOBAR PNEUMONIA

A CLINICAL AND BACTERIOLOGIC STUDY OF TWO THOUSAND TYPED CASES *

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The biologic classification of pneumococci has been a great stimulus to the bacteriologic study of pneumonia and to efforts directed toward the perfection of an efficient serum treatment for this disease. This classification is a result of the work of several investigators, the chief of whom are Neufeld [1] and Lister [2] abroad, and Dochez and Gillespie [3] in this country. The differentiation of pneumococci into types is based on their capacity to produce specific agglutinins, precipitins and protective bodies. The investigators at the Rockefeller Institute in their original studies found that there were three dominant biologic types of pneumococcus, each possessing specific and characteristic immune reactions. In their experience, the organisms of these three types comprised about 80 per cent of all strains encountered in patients with pneumonia, and represented apparently fixed types of a highly parasitic nature. These three types have been referred to as types I, II and III. In the remaining 20 per cent of their patients they found pneumococci which they referred to collectively as pneumococcus type IV. This group is really an assembly of all other types of pneumococcus, many of them just as distinct as types I, II and III. At first, it was thought that each individual strain of pneumococcus type IV was immunologically distinct, but Olmstead [4] has shown that certain strains may have common

* From the Second Medical (Cornell) Division and the Pathological Department of Bellevue Hospital. This investigation received financial aid from the Influenza Fund of the Metropolitan Life Insurance Company.

1. Neufeld, F., and Handel: Ueber die Entstehung der Krisis bei der Pneumonie und uber die Wirkung des Pneumokokkenimmunserums, Arb. a. d. k. Gsndhtsamte. **34**:166, 1910.

2. Lister, F. S.: Specific Serological Reactions with Pneumococci from Different Sources, South African Inst. M. Research, Pub. 2, 1913.

3. Dochez, A. R., and Gillespie, L. J.: A Biologic Classification of Pneumococci by Means of Immunity Reactions, J. A. M. A. **61**:727 (Sept. 6) 1913.

4. Olmstead, M.: An Antigenic Classification of the Group IV Pneumococci, J. Immunol. **2**:425, 1917.

characters, thus proving that there are definite subgroups in the type IV group of pneumococci. The type IV group is sometimes referred to as the "waste-basket" group, because it contains all pneumococci not included in the three fixed types. Pneumococci of the type IV group are the organisms most frequently encountered in the mouth secretions of healthy persons.

Dochez and his co-workers determined the incidence and death rate for the four so-called types of pneumococcus, and the more recent studies of Avery,[5] Stillman[6] and others have thrown considerable light on the epidemiology of the disease with respect to the various types. So far as we know, however, little effort has been made to correlate the type of pneumococcus with clinical manifestations, complications and other features of the disease.

During the past five years more than 2,000 patients with lobar pneumonia have been admitted to the medical wards of the Bellevue Hospital. Through the kind cooperation of the directors of the four medical services, the cases of all patients with lobar pneumonia admitted to the medical wards have been carefully studied from both the bacteriologic and clinical standpoint. With possibly a few exceptions, each person included in this series of 2,000 patients was seen and examined by one of us. A complete résumé of the history of each patient, including pathologic observations in case of autopsy, was kept on large filing cards. On the same card a complete record of the bacteriologic observations, including those made on examination of the sputum, blood culture and during other examinations, was also recorded.

SELECTION AND DISTRIBUTION OF CASES

All cases of clinical pneumonia which showed frank signs of consolidation were included in the series. Practically all of these were lobar in type. Such cases were counted even though cultures failed to reveal pneumococci. A few cases of pneumococcus and streptococcus pneumonia were encountered in which the physical signs were not absolutely frank, but in which the patient presented the cardinal symptoms (chill, fever, pain in side and cough with rusty sputum) of lobar pneumonia. They were, therefore, included in the series.

Race and Color.—As Bellevue Hospital is a city institution and receives its patients chiefly from the East Side of New York, it was to be expected that all races and practically all nationalities would be represented in this series of cases. Such proved to be the case. The nationality was mentioned in 980 cases. Of these, 40 per cent were born

5. Dochez, A. R., and Avery, O. T.: The Occurrence of Carriers of Disease-Producing Types of Pneumococcus, J. Exper. Med. **22**:105, 1915.

6. Stillman, E. G.: A Contribution to the Epidemiology of Lobar Pneumonia, J. Exper. Med. **26**:651, 1916.

in the United States and 15 per cent of these were negroes. Next in frequency were the Irish and Italians, constituting, respectively, 10 and 5 per cent of the total series. The remaining 45 per cent were divided among the various nations of Europe, Asia and South America. Apparently no race is immune to pneumonia.

Occupation.—Of 873 patients, the vocation was mentioned on the filing card of 328. Two hundred and twelve of these, or 64 per cent, were engaged in outdoor occupations. Sailors and day laborers led the list and were about equally represented, constituting together more than half of the entire outdoor group. Ninety per cent of the 209 women patients were housewives, and could therefore be classified as indoor workers.

TABLE 1.—*Distribution by Age*

Decade	Number of Cases	Percentage of Incidence
Under 20	134	7.1
20 to 30	451	24.1
30 to 40	487	26.0
40 to 50	393	21.0
50 to 60	239	12.7
60 and over	163	8.7

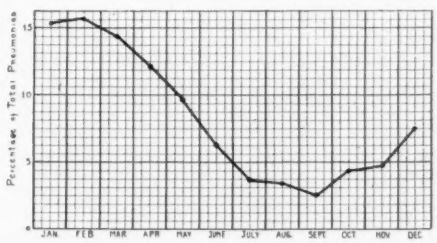

Chart 1.—Monthly incidence of cases of lobar pneumonia in Bellevue Hospital.

Sex.—In 1,867 cases of pneumococcus pneumonia, 1,550 (83.1 per cent) occurred in men, and 317 (16.9 per cent) in women. The incidence rate of pneumonia has always been higher in men than in women, presumably because of their greater exposure to wet and cold. The greater frequency of alcoholism among men also plays some part.

Age.—About one half of the present series of cases occurred in patients between 20 and 40 years of age. This was to be expected in view of the fact that the patients in Bellevue Hospital are largely recruited from the laboring classes. The actual incidence percentage for each decade is shown in table 1.

Season.—January, February and March are the pneumonia months in New York City. The number of patients (1,195) admitted during

these three months, for the five year period covered by this study, constituted nearly one half of the entire series of cases. The number of admissions for pneumonia for April was distinctly higher than that for December. July, August and September showed the lowest incidence with a total for the three months of only 253 cases. When the incidence of pneumonia by month is plotted (chart 1), there is seen a steady and regular drop in the curve from February to September. In October the curve begins to rise slightly, and continues to rise gradually through the autumn and winter until January, when it takes a sharp rise to the maximum. The actual number of admissions during each month is shown in table 2.

TABLE 2.—*Incidence per Month*

	Cases	Percentage of Incidence
January	406	15.4
February	414	15.7
March	375	14.2
April	311	11.8
May	254	9.6
June	173	6.5
July	93	3.5
August	86	3.2
September	74	2.8
October	113	4.2
November	125	4.7
December	205	7.7
Total cases	2,629	

PREDISPOSING FACTORS AND CAUSES

Etiology.—No accurate record was available in respect to the part actually played by exposure, fatigue and other conditions as predisposing etiologic factors. It may safely be said, however, that of such factors, exposure to cold and wet was the most important and was mentioned in the history of a considerable number of the cases. According to the histories, pneumonia followed some acute infection of the upper respiratory tract in 46.7 per cent of the cases of pneumococcus infection. This figure should undoubtedly be higher, as many of the patients were too sick to be questioned carefully. Of 1,002 cases carefully investigated regarding the coexistence of some constitutional disorder, chronic systemic disease, including alcoholism, was found to be a predisposing factor in 32.6 per cent. Alcohol played a rather small part as a predisposing factor. This was probably due to the fact that many of the cases of alcoholic pneumonia were admitted to the alcoholic wards, the material from which was not included in this study.

Exciting Causes: Bacteriology.—An effort was made to determine the type of infection in every case of pneumonia in the series. This determination was usually made from the sputum. In a few instances, no sputum was available and recourse was had to pharyngeal swabs, blood cultures, pleural fluid or postmortem cultures from the lungs. In certain

severe cases, the type of pneumococcus was determined by performing precipitin tests on the urine. Puncture of the lung was never resorted to in living patients, but was frequently employed after death for the purpose of making a bacteriologic diagnosis, or for controlling cultures previously made from the sputum. Fresh sputum for examination was collected in sterile bottles or Petri dishes. Smears were made and stained by the Gram method, in some cases by Hiss' capsule stain. In all cases in which tuberculosis was suspected, a search was made for the tubercle bacillus.

The mouse method was used almost exclusively in the bacteriologic examination of the sputum. Agglutination and precipitation tests were performed with the mouse exudate, and at the same time cultures were made on blood agar plates from both the heart blood and peritoneum of the mouse. Whenever the readings from the mouse exudate indicated pneumococcus type IV or an atypical pneumococcus type II, colonies were fished from the plates, and the pneumococcus was retyped from the

TABLE 3.—*Bacteriologic Classification of 2,000 Cases of Lobar Pneumonia*

Bacteria	Cases	Percentage of Incidence
Pneumococcus	1,913	95.65
Hemolytic streptococcus	76	3.8
Friedländer bacillus	8	0.4
Influenza bacillus	1	0.05
Staphylococcus aureus	2	0.1
Total	2,000	

broth culture. Typings from cultures were also made whenever the mouse exudate gave a doubtful reaction. In a majority of the fatal cases, the bacteriologic examination of the sputum was controlled by postmortem cultures. Failure to make a bacteriologic diagnosis was due to lack of sputum, absence of pathogenic bacteria in cultures from the sputum, or death and removal of the body from the hospital before cultures could be taken. Cases in which a satisfactory bacteriologic examination could not be made have been excluded from this series.

In table 3, the 2,000 cases included in the present study have been classified according to the type of micro-organism isolated. In cases of mixed infection the pneumococcus has been given preference; for example, if the sputum showed both pneumococcus and streptococcus, the case has been classified as a pneumococcus pneumonia. Cases in which the pneumococcus was absent and in which the streptococcus was associated with the influenza bacillus have been classified as streptococcic pneumonia.

Of the 2,000 classified cases, 1,913, or 95.65 per cent, showed some type of pneumococcus; 3.8 per cent were apparently due to *Streptococcus hemolyticus*. It is probable that a large number of the latter group

were originally pneumococcus infections, and that the streptococcus, acting as a secondary invader, had entirely replaced the pneumococcus at the time the cultures were taken. Such a transformation in the bacterial flora of the sputum was actually demonstrated in more than one instance. There was one case in which *Bacillus influenzae* was isolated in pure culture from the sputum. Eight cases were due to Friedländer's bacillus, and two cases were apparently caused by *Staphylococcus aureus*. The propriety of considering any case of pneumonia as "lobar" in which no pneumococci are demonstrable is, of course, a question open to much debate. The remainder of this study will be confined almost entirely to the pneumococcic cases.

Table 4 shows the incidence of the various types of pneumococcic pneumonia. Of a total of 1,913 cases of pneumococcic pneumonia, 644, or 33.6 per cent, showed pneumococcus type I; 368, or 19.1 per cent, pneumococcus type II; 268, or 13.3 per cent, pneumococcus type III; and 633, or 33.1 per cent, pneumococcus type IV. When these figures

TABLE 4.—*Incidence by Type in 1,913 Cases of Pneumococcic Pneumonia*

Type of Pneumococcus	Cases	Percentage of Incidence
I	644	33.6
II	368	19.1
III	268	13.3
IV	633	33.1

are compared with those of Dochez and Gillespie, it will be seen that the incidence of type IV pneumonia in the present series is higher than theirs, while that of type II is distinctly lower. The reason for this discrepancy is not clear, but can probably be explained on the basis of a difference in the character of patients studied in the two series.

TYPES OF PNEUMOCOCCUS

Yearly Variations in Incidence.—The incidence of the four types of pneumococcus undoubtedly varies within certain limits from year to year. In the present series, for example, the rate of incidence for pneumococcus type I pneumonia was 45.2 per cent during the season of 1920-1921, while for 1922-1923, type I pneumococcus was the cause of only 21 per cent of the cases. The incidence by type for each of the five years covered by this study is shown in table 5.

The incidence of types II and III showed comparatively small variations during the five years of observation. During epidemics of influenza there is always a marked increase in the incidence of pneumococcus type IV pneumonia. This is doubtless due to the fact that postinfluenzal pneumonia is essentially a secondary infection. While the primary infection with the influenza virus comes from without, the secondary infection

is probably autogenous; that is, it is referable to one of the comparatively avirulent strains of pneumococcus type IV which so many healthy persons carry in their own buccal cavities.

There is apparently no relation between season and the incidence of the various types of pneumococcic pneumonia. All types occurred in

TABLE 5.—*Variation of Yearly Incidence in Pneumococcus Pneumonia*

Period	Type	Cases	Percentage of Incidence
1920-1921	I	166	45.2
	II	68	15.9
	III	54	14.5
	IV	89	23.5
	Total	377	
1921-1922	I	180	33.7
	II	97	18.1
	III	83	15.7
	IV	174	32.5
	Total	534	
1922-1923	I	67	21.0
	II	66	20.6
	III	55	17.2
	IV	131	41.0
	Total	319	
1923-1924	I	85	30.9
	II	55	20.0
	III	44	16.0
	IV	91	33.0
	Total	275	
1924-1925	I	146	35.7
	II	82	20.0
	III	32	7.9
	IV	148	36.2
	Total	408	

TABLE 6.—*Incidence of Types in Relation to Age*

Type of Pneumococcus	From 10 to 20 Years		Under 30 Years		Under 40 Years		Under 50 Years		Over 50 Years		Over 60 Years	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
I	59	45.5	246	42.0	323	33.2	535	36.5	92	22.8	32	20.0
II	16	11.9	105	17.9	196	20.2	280	12.2	82	23.9	22	13.7
III	8	5.9	41	7.0	103	10.6	166	11.3	97	24.1	54	33.7
IV	51	38.0	193	32.9	348	33.6	484	32.6	131	32.6	55	34.1
	134	7.1	585	31.3	970	51.9	1,465	78.4	402	21.5	163	8.5

both winter and summer. Streptococcic pneumonia, like pneumonia caused by pneumococcus type IV, is usually a secondary infection, and is, for the most part, a winter and spring infection.

RELATION OF TYPES TO AGE

In table 6 some interesting facts are brought out concerning the relation of age to the incidence of the four types of pneumococcic pneumonia.

According to these figures, young people are particularly prone to pneumococcus type I pneumonia, while the elderly are especially susceptible to pneumococcus type III pneumonia. Type I infections are extremely common in the second decade, constituting 45.5 per cent of all pneumococcic infections occurring in patients between 10 and 20 years of age. In patients under 30, 42 per cent show type I infections. As each succeeding decade is added, the incidence of type I falls, and when the plus sixty group is reached, pneumococcus type I infections constitute only 20 per cent of the entire series. Just the reverse happens with pneumococcus type III. Between the ages of 10 and 20, type III infections comprise only 5.9 per cent of the series. With each succeeding decade, however, the incidence increases, and in the sixty plus group, pneumococcus type III pneumonia constitutes 33.7 per cent of pneumococcic pneumonias occurring at this period of life. In contrast to these two groups, type II and type IV show no special predilection for any age group. The incidence of type IV for the various periods of life is remarkably constant (32.6 to 38 per cent).

TABLE 7.—*Incidence of Types in Relation to Sex*

Type of Pneumococcus	Total Men		Total Women	
	Cases	Per Cent	Cases	Per Cent
I	545	35.1	82	25.8
II	312	20.2	50	15.7
III	194	12.5	69	21.8
IV	499	32.2	116	36.6
Total	1,550		317	

INCIDENCE OF TYPES IN RELATION TO SEX

Women constituted only 16.9 per cent of all the cases of pneumococcic pneumonias that were studied. Table 7 shows the relative incidence of the various types in men and in women.

According to these figures, pneumococcus type I is relatively much commoner in men than in women (35.1 per cent against 25.8 per cent). The same is true, but to a less extent, of type II. Type III, on the other hand, is almost twice as common in women as in men, and type IV shows a slight preference for the women (36.6 in women and 32.2 in men).

Incidence of Type in Relation to Age and Sex.—When the two factors of age and sex are combined in one table (table 8), their effect on the incidence of the various types is strikingly displayed. For example, type I is three times as common in men under 50 as in women over 50 (37.8 vs. 12 per cent). Type II shows a similar but less striking divergence (19.3 vs. 8.3 per cent). On the other hand, type III is nearly four times as common in women over 50 as in men under 50 (36.1 vs.

10.1 per cent), and type IV is commoner in elderly women than in young men. Summarizing, 57.1 per cent of the cases of lobar pneumonia in men under 50 were either type I or type II; 77.7 per cent of the cases of lobar pneumonia in women over 50 were type III or type IV.

MIXED INFECTIONS

A mixed bacterial flora is not uncommon in pneumonic sputum. The idea is prevalent that mixed infections are associated with bronchopneumonia, usually of the influenzal type, and it is true that most cases of bronchopneumonia showed a mixed bacterial flora. In lobar pneumonia, however, it is not unusual to find the pneumococcus associated in the sputum with some other pathogenic organism. In table 9 the number of pure and mixed infections occurring with each type are compared. These observations are based almost entirely on bacteriologic examinations of sputum.

TABLE 8.—*Incidence of Types in Relation to Sex and Age*

Type of Pneumococcus	Men Under 50 Years		Women Under 50 Years		Men Over 50 Years		Women Over 50 Years	
	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
I	462	37.8	73	29.7	83	25.1	9	12.0
II	236	19.3	44	17.9	76	23.0	6	8.3
III	124	10.1	42	17.1	70	21.2	27	36.1
IV	398	32.5	86	35.1	101	30.6	30	41.6
Total	1,220		245		330		72	

TABLE 9.—*Incidence of Mixed Flora in 1,913 Cases of Pneumococcus Pneumonia in Relation to Types*

Type of Pneumococcus	Total	Mixed	Percentage of Mixed
I	644	119	18.4
II	368	87	23.6
III	268	64	23.9
IV	633	199	31.2
	1,913	469	24.5

The percentage of mixed infections varies for the types, being lowest in type I cases (18.4 per cent) and highest in the type IV group (31.2 per cent).

Mixed infections are commoner some years than others. For example, the incidence of mixed infections showed a much higher rate in the winter of 1921-1922 than in 1920-1921, possibly on account of the influenza epidemic that appeared in January and February of 1922. The figures are shown in table 10. The incidence of mixed infection was more than four times as common in 1921-1922 as in 1920-1921.

In table 11 the mixed infections are classified according to the bacteria isolated.

By far the commonest mixed flora was that of pneumococcus and the influenza bacillus. Altogether, there were 330 cases of pneumococcic pneumonia that also showed influenza bacilli in the sputum (17.4 per cent). Next in frequency was the combination of pneumococcus with *Streptococcus hemolyticus*. The isolation of two different types of pneumococcus from the same case was an interesting bacteriologic observation. In some instances they were isolated from the same specimen of sputum; in others, from different specimens. When they occurred in the same specimen, one was probably an accidental observation. When in separate specimens, the possibility of a superinfection had to be considered.

TABLE 10.—*Incidence of Infection According to Seasons*

Type of Pneumococcus	Season of 1920-1921			Season of 1921-1922		
	Pure	Mixed	Percentage of Mixed	Pure	Mixed	Percentage of Mixed
I	137	16	10.4	86	82	48.8
II	58	8	12.1	37	55	59.7
III	44	4	8.3	39	37	48.6
IV	68	12	15.0	74	89	54.6
Total	307	40	11.5	236	263	52.7

TABLE 11.—*Bacteria Found in Mixed Infections*

Pneumococcus and Bacillus influenzae	330
Pneumococcus and Streptococcus hemolyticus	82
Pneumococcus, Bacillus influenzae and Streptococcus hemolyticus	28
Pneumococcus, Bacillus influenzae and nonhemolytic streptococcus	5
Pneumococcus type I and pneumococcus type III	1
Pneumococcus type I and pneumococcus type IV	4
Pneumococcus type III and pneumococcus type IV	7
Pneumococcus and tubercle bacillus	4
Pneumococcus and Friedländer's bacillus	9
Total	470

One of the most surprising observations in this connection was the comparatively low incidence of active pulmonary tuberculosis in association with lobar pneumonia. This is consistent with the experience at Saranac Lake and other sanatoriums for the tuberculous, in which lobar pneumonia is rarely encountered among the tuberculous patients. Bronchopneumonia is, of course, often seen as a terminal infection in tuberculosis, but for some reason, frank lobar consolidations are infrequent.

The combination of streptococcus with the influenza bacillus is a common observation in bronchopneumonia, particularly the postinfluenzal type, but is rarely seen in frank lobar pneumonia. *Streptococcus hemolyticus* is probably capable of setting up a true lobar consolidation, though it rarely does so. It is extremely doubtful whether the influenza bacillus ever produces a lobar type of infection. Pneumococcus was

found with both the *Streptococcus hemolyticus* and the influenza bacillus in twenty-eight cases. In nine cases the pneumococcus occurred in association with Friedländer's bacillus. In the latter group, the question arises whether these were genuine mixed infections, or whether the Friedländer bacillus was a purely accidental observation. Indeed, the same question comes up with all the so-called mixed infections (pneumococcus plus tubercle bacillus excepted). Undoubtedly, *Streptococcus hemolyticus* plays an important part as secondary invader in many cases, but the evidence for Pfeiffer's bacillus is not convincing. In respect to death rate and complications, it has been found that the presence of influenza bacilli in the sputum of patients with pneumococcic pneumonia has little effect on either the mortality rate or the incidence of complications.

PRIMARY AND SECONDARY LOBAR PNEUMONIA

Bacteriology.—Lobar pneumonia as regards onset can be divided into two large groups—primary pneumonia and pneumonia secondary to some infection of the upper respiratory tract. In making this differentiation only those cases could be counted in which a coherent history was obtainable from the patient or from his family. Even under these conditions, the figures are only approximately correct. Patients of low intelligence are often hazy on the subject of coryza and sore throats, and these two conditions are the commonest predisposing infections. Other patients gave a history of a preceding influenza, bronchitis, tonsillitis, otitis media, asthma or pulmonary tuberculosis.

TABLE 12.—*Relation of Types to Primary and Secondary Pneumonia*

Type of Pneumococcus	Total Cases	Primary Cases	Percentage Primary	Secondary Cases	Percentage Secondary
I.....	627	401	63.9	226	36.0
II.....	310	173	55.7	137	44.2
III.....	209	92	44.0	117	55.9
IV.....	508	214	42.1	294	58.8
Total.....	1,654	880	53.2	774	46.7

According to table 12, 46.7 per cent of the cases of pneumonia were secondary to some preceding respiratory infection. This figure is probably much too low, but we doubt whether more than 70 per cent, at most, of all cases of lobar pneumonia are secondary infections. If it is assumed that the percentage of error was about the same for the different groups, interesting variations are observed. The incidence of secondary pneumonia is lowest in the pneumococcus type 1 group (36 per cent), and increases with each group until in group IV 58.8 per cent of the cases are secondary. It was to be expected that secondary pneumonia would occur more frequently in the type III and type IV groups than in the type I and type II groups, as the former are not

uncommonly found as inhabitants of the normal mouth. Pneumococcus type I and type II are almost never encountered in the healthy mouth.

Mixed Infections.—If the finding of two different species of bacteria in the sputum of a patient with pneumonia really means a double infection, one would perhaps expect to find the incidence of mixed infections higher in pneumonia secondary to some respiratory infection than in primary pneumonia. Such, however, does not prove to be the case, as is shown in table 13.

In the primary infections 29.8 per cent of the pneumococcic cases showed a mixed flora, while in the cases of secondary pneumonia 27.1 per cent presented more than one species of pathogenic microorganism.

TABLE 13.—*Mixed Flora in Primary and in Secondary Pneumonia*

	Primary			Secondary		
Type of Pneumococcus	Total	Mixed	Percentage of Mixed	Total	Mixed	Percentage of Mixed
I	401	74	18.4	223	45	19.9
II	173	49	28.3	137	38	27.8
III	92	38	41.3	117	26	22.0
IV	214	96	44.8	294	101	34.3
	880	257	29.8	774	210	27.1

TABLE 14.—*Incidence of Systemic Disease by Type*

Type	Cases	Systemic Disease	Percentage of Incidence
I	298	61	20.4
II	203	67	33.0
III	131	83	63.3
IV	370	116	31.3
Total	1,002	327	32.6

LOBAR PNEUMONIA IN PATIENTS WITH CHRONIC SYSTEMIC DISEASE

In patients suffering from some chronic constitutional disease, lobar pneumonia may occur as a primary infection or secondary to some preceding respiratory disease. A few of these cases of pneumonia are embolic in origin and develop from septic infarcts. The majority are bronchogenic infections, the sequelae of diminished vitality and resistance.

Incidence of Systemic Disease in Association with the Various Types of Pneumococcus.—Table 14 shows the incidence of systemic disease in association with each type. Thirty-two and six tenths per cent of this series occurred in patients with systemic disease. Strangely enough, the incidence of systemic disease was strikingly higher in the type III group than in any of the other groups, being three times as high as it

was in the type I group. It has already been shown that elderly people are particularly susceptible to type III pneumonia. Whether the frequency of systemic disease in the elderly is responsible for this susceptibility is not known, but the figures presented in the foregoing suggest such an explanation. Type III pneumonia is extremely common in institutions for the insane.

CHARACTERISTICS OF DISEASE

Symptomatology.—A statistical study of the symptoms of pneumonia as seen in a city hospital is subject to error by reason of the fact that patients are admitted at all stages of the disease. This handicap can be overcome in part by the taking of careful histories, but even then the ignorance of some patients, the inability of others to speak English, the presence of delirium, coma and other factors interfere with the collection of accurate data on the subjective symptoms of the disease.

Day of Admission.—A comparatively small number of patients with lobar pneumonia are admitted to Bellevue Hospital during the first forty-eight hours of the disease (from 15 to 20 per cent). The largest number of patients come in on the third and fourth days of their infection.

Character of Onset.—The onset of lobar pneumonia is one of the most characteristic features of the disease. In a large majority of cases a diagnosis of pneumonia can be made from a history of the onset alone. As previously pointed out, it may or may not follow an infection of the upper respiratory tract, but in either case, the one quality which distinguishes the onset of pneumonia is its suddenness. There are exceptions, of course, in which the symptoms come on gradually, but in the great majority of cases, the onset of lobar pneumonia is strikingly sudden. The five cardinal symptoms are chill, fever, pain in the side, cough and expectoration of rusty sputum. Of these the chill is usually the first to appear, the pain in the side coming shortly after. Neither the chill nor the pain in the side is present in every case. Fever is present in practically 100 per cent of the cases, though some old people show only a slight elevation of temperature. Cough is present in more than 90 per cent of the cases, but is not always accompanied by rusty sputum. In respect to the other cardinal symptoms, it is interesting to observe how their incidence varied with different types (figures based on the first 1,000 cases of the series).

Pain in the side was mentioned as a symptom in more than 80 per cent of all cases falling in the three fixed groups. The incidence of pain was distinctly lower in the type IV series (approximately 60 per cent).

The chill occurred most frequently in cases of pneumococcus type I (70 per cent), and least frequently in cases of pneumococcus type IV (55 per cent). These figures do not include "chilly sensations."

Rusty sputum is one of the most important signs of lobar pneumonia, not only from the diagnostic, but also from the prognostic standpoint. Its presence is almost pathognomonic, and as long as it persists, one can usually assume that the process in the lungs is still active. Bloody or rusty sputum means engorgement or red hepatization, and as these symptoms represent the earlier stages of infection, it may be safely assumed that blood in the expectoration means an actively extending process. Purulent sputum is usually an expression of gray hepatization or resolution, the latter stages of the infection. The disappearance of rusty sputum is therefore a good omen, if complications can be excluded. Rusty sputum was mentioned in the history or laboratory notes of from 55 to 60 per cent of all the cases in the first three groups —about the same proportion in each group. It was reported in only 40 per cent of the type IV cases. These figures certainly should be higher for all types, but the percentage of error is probably about the

TABLE 15.—*Lobes Involved in 1,896 Cases of Pneumococcus Pneumonia*

Type	Right Lower	Right Middle	Right Upper	Left Lower	Left Upper	Two Right Lower	Two Left Lower	Three Right Lower	Right Lower Left Lower	Third Lobes	Four Lobes
I.....	138	9	36	174	18	59	27	44	88	33	6
II.....	82	4	29	85	14	37	19	12	54	21	8
III.....	70	4	11	60	11	29	18	6	59	6	3
IV.....	150	11	41	186	25	38	29	10	107	22	12
Total...	440	28	117	505	68	154	93	72	308	82	29

same in each group. Apparently the incidence of rusty sputum is approximately the same for the three fixed types, with a distinctly lower incidence in the type IV group.

It is hardly necessary, in an investigation of this kind, to enter into a detailed study of the various other symptoms which were observed. There are certain symptoms whose presence is largely dependent on the severity of the infection, such as dyspnea, cyanosis, weakness, delirium. Headache and general muscular aching rarely occur with lobar pneumonia, but are more frequently seen in the influenzal type of pneumonia. Nausea and vomiting are fairly common symptoms and may be due to several causes: toxemia, anoxemia, digitalization or possibly improper diet.

Lobes Involved.—In the studies of lobar pneumonia conducted by previous investigators, the right lower lobe has been found to be involved more frequently than any other. In table 15 is shown the lobes involved in the present study.

The left lower lobe was involved more frequently than any other in the infections of a single lobe (505 cases), the right lower lobe coming second (440 cases). The right side, however, was involved more fre-

quently than the left side (1,119 to 974 cases). By far the commonest of the two-lobe infections was the combination of right and left lower lobes (308 cases).

The type of infectious agent appears to bear no relation to the lobe or to the extent of the infection. Three and four lobe infections were relatively about as frequent in the milder types (types I and IV) as in the severe types (types II and III of pneumonia).

Pleuritic friction rubs were frequently noted, usually early in the disease and in all types. We have no reliable figures for the relative incidence of herpes, flushed cheeks, jaundice, cardiac enlargement and other well recognized physical observations in lobar pneumonia.

Leukocytes in Lobar Pneumonia.—In almost two thirds of our cases, one or more blood counts were taken during the active stage of the disease. A "composite" leukocyte count based on the counts of patients that received no specific treatment shows an initial rise on the first day, averaging about 20,000 leukocytes. On the second day the count is

TABLE 16.—*Results of Blood Cultures in 329 Cases of Pneumococcic Pneumonia*

Type of Pneumococcus	Number Cultured	Number Positive	Percentage
I	125	33	26.4
II	75	31	39.7
III	36	10	27.7
IV	90	15	16.6
Total	326	89	24.0

higher, and on the third day the peak is usually reached. After the third day, the counts are lower but still considerably above normal. In a monkey with experimental pneumococcic pneumonia, the peak is often reached on the second day of the disease, and the same may happen in the case of man.

In fatal cases with septicemia the leukocyte count in both monkey and man is usually below normal, especially toward the end, unless a complication is present, in which case there may be a secondary rise in the curve.

Pneumococcic Bacteremia.—Blood cultures were taken in 329 cases in this series.

Technic.—In most cases from 1 to 5 cc. of blood was drawn directly into plain broth. One cubic centimeter was plated out in agar in order that the number of colonies per cubic centimeter of blood could be determined.

Of the 329 cases in which cultures were taken, eighty-nine, or 24 per cent, showed some type of pneumococcus in the blood. The incidence of septicemia was much higher (34.5 per cent) in 107 cases in which cultures were taken repeatedly during the course of the disease

(table 25). As might have been expected, the incidence of septicemia was higher in the severe types (II and III) than in the mild types (I and IV). Type II pneumonia is essentially the pneumonia of septicemia, yielding positive blood cultures more than twice as frequently as type IV infections.

Urinalysis and Roentgen-Ray Examination.—Practically every case showed albumin with or without casts at some stage of the disease. In only a small percentage of the cases studied in this series were the patients examined by roentgen ray. The number was too small for analysis.

COURSE OF DISEASE

No striking features in the clinical course could be demonstrated as characteristic of the various types of pneumonia. The temperature is more apt to be irregular in type IV pneumonia than in the three fixed

TABLE 17.—*Duration of Disease in Untreated Patients Who Recovered*

Type	Cases	Average No. of Days
I	264	8.8
II	117	8.6
III	85	9.1
IV	226	8.7
Total	692	8.8

TABLE 18.—*Incidence of Crisis and Lysis in Untreated Patients*

Type of Pneumococcus	Total Cases	Crisis	Lysis	Percentage With Crisis
I	285	146	112	56.6
II	122	61	61	50.0
III	89	35	54	39.3
IV	248	113	135	45.5
	744	355	362	49.6

types of infection, in which a high and fairly level plateau is the general rule. However, there are numerous exceptions in all groups.

Duration of Disease.—It was interesting to compare the duration of pneumonia (as measured by fever) for the various types. Table 17 shows the average duration for each type, dating from the day of chill or pain in the side to the first day of a rectal temperature of 100 F. or less. The figures are based on a series of 692 consecutive cases, in none of which the patient was treated with serum. Cases in which complications developed have been excluded.

Pneumococcus type III pneumonia runs a somewhat longer course than the other types. This characteristic was even more strikingly evident in our studies of experimental pneumonia in monkeys.

Mode of Termination.—Lobar pneumonia terminates by either crisis or lysis. Table 18 shows the incidence of crisis and lysis for each type

in 717 cases of pneumonia in which the patient received no specific treatment.

Crisis occurred most frequently in type I infections (56.6 per cent). The incidence of crisis in type III was much lower, only 39.3 per cent. Types II and IV occupied intermediate positions.

DEATH RATE

The death rate in pneumonia is dependent on a great many factors. A number of these factors will be considered with special reference to the influence of pneumococcus type.

Effect of Season on Death Rate.—Before analyzing the effect of the pneumococcic type on the death rate of pneumonia, it may be worth while to show how the mortality rate in pneumonia is affected by season.

TABLE 19.—*Percentage Mortality by Month*

Month.	Cases		Died		Percentage Fatal	
January	406	1,195	152	421	37.4	35.2
February	414		160		38.6	
March	375		109		29.0	
April	311		90		28.9	
May	254		61		24.0	
June	173		33		19.0	
July	93	253	26	69	27.9	27.2
August	86		18		20.9	
September	74		25		33.7	
October	113		43		38.0	
November	125		40		32.0	
December	206		68		33.1	
Total	2,629		825		31.7	

In table 19, the incidence of pneumonia by month, with the number of deaths, is indicated for a period covering about five years. In this table, it will be seen that there is a considerable difference in the death rate between the group of cases which occurred during the season that pneumonia was most prevalent (January, February and March) and the group of cases that occurred during the season that it was least prevalent (July, August and September). In the former group of 1,195 cases, the death rate was 35.2 per cent; whereas, in the latter group of 253 cases, the death rate was only 27.2 per cent, 8 per cent less than that for the winter months. Pneumonia, therefore, is not only more frequent in the winter, but appears to be more serious also. This may be due to several factors, such as increased virulence of the organism or lower resistance of the patient.

Variation in Mortality by Year.—In the Bellevue Hospital, the death rate for pneumonia has shown considerable variation from year to year. For instance, in the season of 1920-1921, the death rate was only 24.6 per cent; whereas, in the season of 1923-1924, the death rate was 34.9 per cent, an increase of 10 per cent. This variation in death rate

from year to year does not appear to be dependent entirely on variations in the incidence of types. So many factors enter into the problem that it would be dangerous to say which of them exercises the dominant influence in determining the death rate for any particular season.

Death Rate According to Type.—Table 21 shows the death rate for the various types. As each group consists of a hundred or more

TABLE 20.—*Variations in Yearly Mortality Rates*

Period	Type	Patients Died	Percentage of Mortality
1920-1921	I	34	20.4
	II	20	29.4
	III	19	35.2
	IV	20	22.4
	Total	93	24.6
1921-1922	I	31	17.1
	II	38	39.3
	III	36	43.3
	IV	33	18.9
	Total	138	25.8
1922-1923	I	8	11.9
	II	26	39.8
	III	22	40.0
	IV	33	25.1
	Total	89	27.9
1923-1924	I	17	20.0
	II	28	50.9
	III	20	45.4
	IV	31	34.0
	Total	96	34.9
1924-1925	I	32	21.9
	II	34	41.4
	III	17	53.1
	IV	45	30.4
	Total	128	31.3

TABLE 21.—*Death Rate According to Type in Pneumococcic Pneumonia*

Type of Pneumococcus	(No Specific Treatment) Cases	Died	Per Cent
I	352	73	20.7
II	221	93	42.0
III	161	67	41.6
IV	373	109	29.2
	1,107	342	30.8

cases, these figures should be reliable. Only those patients have been included in this table who received no specific therapy.

The death rate for type I pneumonia, even when no serum is given, is lower than that of any of the other types. No doubt this low figure (20.7 per cent) is due in large measure to the fact, previously brought out, that type I pneumonia is the pneumonia of young people. This figure is considerably lower than that given by Cole [7] for type I pneumonia (not treated with serum) at the Rockefeller Institute.

7. Cole, R.: Nelson's Loose-Leaf Living Medicine **1**:203, 1920.

The death rate for 221 cases of pneumococcus type II pneumonia in our series was 42 per cent; in other words, it proved to be the most virulent of the four types. Our figure is much higher than that of Cole, whose series of cases of type II pneumonia showed a death rate of only 29.5 per cent. After extensive experience with type II pneumonia, we have come to look on it at Bellevue as the most serious form of pneumonia with which we have to deal, and the reason for this is that nearly half of the patients develop a pneumococcic bacteremia. Even allowing for the fact that pneumonia at Bellevue Hospital shows a somewhat higher death rate than that observed in other hospitals, it is probable that Cole's figure of 29.5 per cent is too low.

The death rate for 161 cases of pneumococcus type III pneumonia in our series was 41.6 per cent, almost identical with that observed in the Rockefeller series (44.3 per cent). As we have pointed out previously, it appears that the high death rate in pneumococcus type III is largely dependent on the fact that type III pneumonia is essentially the pneumonia of elderly people. Type III pneumonia in the young is not particularly severe.

The death rate for 373 cases of pneumococcus type IV pneumonia was 29.2 per cent. Type IV pneumonia, like type III, is not necessarily a virulent infection. The death rate for type IV pneumonia in the Rockefeller series was only 13.2 per cent. The number of cases, however, on which this figure is based is not mentioned. The death rate in type IV pneumonia, as in other types, will depend in large part on the kind of patients with which one is dealing; but in our experience, the prognosis in type IV pneumonia is not so good as it has been reported to be, largely because it is the type of pneumonia most frequently seen after influenza and also as a complication of various chronic systemic diseases.

The death rate for the entire series of 1,107 cases of pneumococcic pneumonia in which the patient received no specific treatment was 30.8 per cent, a figure which corresponds rather closely to the usual death rate for lobar pneumonia in city hospitals everywhere.

From these mortality figures, it is evident that types I and IV are the mild forms of pneumonia, while types II and III are almost twice as virulent. In spite of these differences, however, there are more deaths from type I and type IV pneumonia than there are from the type II and III infections, because the mild forms are of so much commoner occurrence.

Mortality in Relation to Age and Type.—The importance of age in the prognosis of pneumonia has long been recognized. In table 22 the relation of age to mortality in the various types of pneumonia is clearly brought out.

It will be observed that in patients under 40 years of age, type III pneumonia is a comparatively mild infection, showing a death rate actually lower than some of the other types. After 40, the death rate for type III becomes high, no higher, however, than that for type II cases in the same age group. All four of the types show a steadily increasing death rate for each decade. This increase in the death rate for each decade is well shown in the total number of cases for each age group. Starting with a mortality rate of 11.1 per cent for patients under 20, it increases steadily with each decade until, in the group of patients over 60 years of age, it has reached a figure of 52.7 per cent.

TABLE 22.—*Mortality in Relation to Age and Type*

Type of Pneumococcus	Under 20 Years		20 to 30 Years		30 to 40 Years		40 to 50 Years		50 to 60 Years		Over 60 Years	
	Cases	Percentage Fatal	Cases	Percentage Fatal	Cases	Percentage Fatal	Cases	Percentage Fatal	Cases	Percentage Fatal	Cases	Percentage Fatal
I	59	8.4	187	16.0	179	17.8	110	21.0	60	26.6	32	31.2
II	16	18.7	80	17.9	91	38.4	84	53.5	60	45.0	22	63.6
III	8	12.5	33	15.1	62	29.0	63	44.4	43	69.7	54	59.2
IV	51	13.6	142	13.3	155	21.2	136	29.4	76	38.1	55	54.5
	134	11.1	451	15.5	487	24.2	393	34.8	239	42.7	163	52.7

TABLE 23.—*Incidence of Positive Blood Cultures in Relation to Type and Outcome*

Type of Pneumococcus	Patients That Recovered			Patients That Died		
	Cases	Positive Blood Culture	Percentage Positive	Cases	Positive Blood Culture	Percentage Positive
I	87	9	10.3	38	24	63.1
II	39	3	7.6	36	28	77.7
III	17	2	11.1	19	8	42.1
IV	64	1	1.5	26	14	53.8
	207	15	7.2	119	74	62.1

Relation of Septicemia to Death Rate.—Septicemia has a pronounced affect on the prognosis in pneumonia. In table 23 the incidence of septicemia in relation to outcome is indicated for the various types. The figures in this table include all cases in which one or more blood cultures were taken during the course of the disease.

In 207 patients that recovered, bacteremia was demonstrated in only 7.2 per cent. In the sixty-four patients with type IV pneumonia that recovered, only one showed a positive blood culture.

In contrast to these figures, 119 patients that died showed pneumococcus bacteremia in 62.1 per cent. In each of the four types the incidence of bacteremia was many times higher in the fatal cases than in those in which the patient recovered.

In table 24, the same fact is brought out in a slightly different way. The death rate in cases that did not show septicemia is compared with the death rate in cases that showed septicemia. Here, again, a striking difference is noted. Two hundred and forty patients whose blood remained sterile showed a death rate of only 18.7 per cent. On the other hand, eighty-nine patients with positive blood cultures showed a death rate of 83.1 per cent.

As regards the different types, it will be seen that septicemia in types II, III and IV nearly always indicates a fatal termination, the death rate being approximately 90 per cent for these groups. The outlook in type I cases with septicemia is not so grave; otherwise, type I

TABLE 24.—*Death Rate in Cases with Sterile Blood Cultures*

	Death Rate in Cases With Sterile Blood Cultures			Death Rate in Cases With Positive Blood Cultures		
Type of Pneumococcus	Cases	Fatal	Per Cent	Cases	Fatal	Per Cent
I	92	14	15.2	33	24	72.7
II	47	8	16.2	31	28	90.3
III	26	11	41.5	10	8	80.0
IV	75	12	16.0	15	14	93.3
	240	45	18.7	89	74	83.1

TABLE 25.—*Relation of Bacteria to Death Rate in Pneumonia*

		Cases Showing Positive Blood Cultures		Cases Showing Sterile Blood Cultures	
Types of Pneumococcus	Cases Studied	Cases	Deaths	Cases	Deaths
I	39	11	6	28	3
II	22	14	13	8	1
III	11	4	3	7	1
IV	35	8	7	27	2
Total	107	37	29 or 78.3%	70	7 or 10%

differs in no respect from the other types, insuring an extremely high death rate among patients who develop pneumococcic septicemia.

The figures presented in tables 23 and 24 are open to one serious criticism in that many of the patients had only one or two blood cultures taken during the course of their disease. Some of these patients may have had a bacteremia before or after the culture was taken.

In table 25 more accurate figures are presented in a series of 107 patients in whom blood cultures were taken at frequent intervals during the course of the disease, in some instances every day.

It will be observed that in all four types the death rate was high in cases in which there were positive blood cultures. The death rate was somewhat lower in the septic type I series than in the other three types, but this difference was probably due to the effect of specific therapy. Furthermore, it will be noted that the incidence of positive blood

cultures in the various types is roughly proportional to their respective death rates. The occurrence of bacteremia in the less virulent type I and type IV infections is comparatively low, while in the more severe type II and type III infections the incidence of bacteremia is distinctly higher. Finally, the total mortality rate for thirty-seven patients with pneumococcic pneumonia and with positive blood cultures was 78.3 per cent, in contrast to a death rate of 10 per cent for seventy patients with sterile blood cultures.

Effect of Systemic Disease on Death Rate.—The death rate in pneumonia is greatly increased when the disease occurs in patients already affected with some chronic systemic disease.

TABLE 26.—*Death Rate for Cases Showing Systemic Disease*

Type	Cases	Died	Percentage Fatal
I	61	23	37.7
II	67	38	56.7
III	83	55	66.3
IV	116	39	33.6
Total	327	155	46.4

TABLE 27.—*Death Rate for Cases without Systemic Disease*

Type	Cases	Died	Percentage Fatal
I	237	37	14.3
II	136	50	36.7
III	48	4	8.5
IV	254	70	27.5
Total	675	161	23.4

In table 26, the death rate for 327 cases of pneumococcic pneumonia associated with systemic disease was 46.4 per cent, a figure greatly in excess of the normal death rate. Furthermore, the death rate for every type was affected. Even in type IV cases, one third of all the patients infected died.

On the other hand, the death rate in cases entirely free from systemic disease was distinctly lower than the usual figure.

In table 27, it will be observed that in a series of 675 cases of pneumonia without systemic disease, the death rate was only 23.4 per cent. The surprising feature about this table is the extremely low death rate in the type III series. In forty-eight cases of type III pneumonia without systemic disease, there were only four deaths, a mortality rate of 8.5 per cent. It has been pointed out earlier in this study that patients with chronic systemic disease are particularly susceptible to type III pneumonia. It is clear, however, that when healthy persons are attacked by the type III pneumococcus, their chances of recovery are excellent.

Relation of Death Rate to the Number of Lobes Involved.—As might be expected, the death rate in pneumonia runs parallel with the number of lobes involved.

In single lobe infections, the death rate in the present series was only 20.9 per cent; in two lobe infections, 36.3 per cent; in three lobe infections, 40.8 per cent; in four lobe infections, 65.5 per cent. This increase in death rate with the number of lobes affected applies to all four types of pneumonia.

TABLE 28.—*Mortality and Lobe Involvement in 1,896 Cases of Pneumococcus Pneumonia*

	Single Lobe			Two Lobes			Three Lobes			Four Lobes		
Type	Cases	Died	Per-centage	Cases	Died	Per-centage	Cases	Died	Per-centage	Cases	Died	Per-centage
I	375	51	12.6	174	43	18.7	77	21	32.3	6	4	33.3
II	214	70	29.6	110	48	37.2	33	16	42.1	8	5	60.0
III	156	55	29.7	97	46	35.9	12	8	50.0	3	1	25.0
IV	413	67	15.5	174	65	36.1	32	18	58.6	19	9	57.1
Total	1,158	243	20.9	555	202	36.3	154	63	40.8	26	19	65.5

TABLE 29.—*Incidence of Pneumococcus Complications in Relation to Type*

Type of Pneumococcus	Cases	Em-pyema	Peri-car-ditis	Endo-car-ditis	Menin-gitis	Arth-ritis	Phle-bitis	Peri-tonitis	Total	Percent-age of Incidence
I	644	44	4	4	14	5	6	1	78	12.1
II	368	13	3	2	6	0	2	0	26	7.0
III	268	10	1	0	3	1	1	1	17	6.3
IV	633	32	2	4	9	2	4	1	54	8.5
	1,913								175	9.1

COMPLICATIONS

Complications in pneumonia are proverbially common. Any sort of an analysis of the complications which occurred in the 2,000 cases of pneumonia included in the present study would constitute an extensive treatise in itself. In the present report, we have limited our observations to the commoner and more serious complications. These are usually caused by the pneumococcus, but occasionally the streptococcus is responsible, when it occurs as a secondary invader.

Incidence of the More Serious Complications in Relation to Type.—In 1,913 cases of pneumococcic pneumonia, serious complications occurred 175 times, an incidence of 9.1 per cent. In table 29 the incidence of the various complications are listed according to type. When two complications developed in the same case, both have been listed.

The striking feature of table 29 is the high incidence of complications in pneumococcus type I pneumonia, 12.1 per cent of the type I cases being complicated by empyema, pericarditis or one of the other severe complications. The other three types developed complications with about equal frequency, 7, 6.3, and 8.5 per cent, respectively. Empyema was by far the commonest complication in all types. Next in frequency came meningitis. The other complications were comparatively rare.

Empyema.—Pneumococcus type I pneumonia showed the highest incidence of empyema—6.8 per cent. The next highest incidence was for type IV (5 per cent), while type II and type III showed an incidence of 3.5 and 3.7 per cent, respectively. The death rate for the entire group of patients with empyema was 38.3 per cent, with only slight

TABLE 30.—*Incidence and Mortality of Empyema in Relation to Type*

Type of Pneumococcus	Total Cases	Cases of Empyema	Percentage of Incidence	Deaths	Death Rate Percentage
I	644	44	6.8	16	36.3
II	368	13	3.5	5	38.4
III	268	10	3.7	3	33.3
IV	633	32	5.0	14	43.7
Total	1,913	99	5.1	38	38.3

TABLE 31.—*Relation of Time of Onset of Empyema to Death Rate*

Onset	Number	Died	Mortality Percentage
Before seventh day	11	10	90.0
Seventh to fourteenth day	27	14	51.8
On and after fourteenth day	61	41	22.9
	99	38	38.3

differences for the various types. It is possible that the high incidence of empyema and other pneumococcus complications in type I pneumonia is dependent on its high prevalence in young people.

An interesting relationship between the mortality rate and the time of development of empyema is shown in table 31. The earlier in the disease the empyema develops, the higher the death rate. In patients that developed empyema before the seventh day of the disease, the rate of mortality was extremely high (90 per cent). When empyema developed between the seventh and fourteenth day after the onset of pneumonia, the death rate was 51.8 per cent. In patients that developed empyema after the fourteenth day, the death rate was only 22.9 per cent. Fortunately, the last group is the largest, constituting nearly two thirds of the entire series. It is particularly in streptococcus pneumonia that empyema develops early, and this fact doubtless accounts in great measure for the high death rate associated with this form of pneumonia. With the

exception of a few patients in whom empyema was diagnosed just before or after death, patients who developed empyema were transferred to the surgical service for thoracotomy. Patients who developed empyema early in the disease were treated by aspiration until their condition warranted surgical intervention.

COMMENT

The analysis of a large group of cases of pneumococcic pneumonia has enabled us to make some interesting and probably safe deductions concerning certain clinical features of the various types. In the course of our studies at Bellevue, a number of these type characteristics were suspected long before statistics were available to prove them. The fact that the various types of pneumonia possess certain characteristics that differentiate them from one another serves to emphasize the importance of the bacteriologic study in every case. The time has come when every case of lobar pneumonia should be typed. This can usually be accomplished by injecting some sputum into a mouse. If sputum is not available, washings from a throat swab should be injected. Blood culture should also be taken, and precipitin tests carried out on the urine.

Just why these differences exist between the four types of pneumococcic pneumonia it is impossible to say. It is difficult to understand why young people should be particularly susceptible to pneumococcus type I, while older people are more readily attacked by pneumococcus type III. It is difficult to explain why serious complications are almost twice as common in type I as in the other types; or why type II and type III pneumonia are almost twice as fatal as type I or IV. Nevertheless, these differences in the types do exist, and it is important for the practitioner to be aware of them. Knowing the type of pneumonia with which he is dealing, the physician at once knows a good deal more about his patient, his chances of recovery, the danger of complications and the feasibility of specific treatment. For these reasons, an exact knowledge of the bacterial nature of the infection has become an indispensable requisite in the treatment of a pneumonic patient.

In this study we have purposely refrained from a discussion of our results with specific and nonspecific therapy. Approximately one third of the 2,000 patients composing this material received some form of specific or nonspecific treatment. A few patients received antipneumococcus serum; a large number received Huntoon's pneumococcus antibody solution; a much smaller number were treated with Felton's concentrated antipneumococcus serum. Specific treatment was not

limited to any one type of pneumococcic pneumonia. Our results with these various agents have been reported in other articles.[8]

SUMMARY

A summary of the more important facts derived from this investigation may be stated as follows:

A bacteriologic classification of 2,000 typed cases of lobar pneumonia showed the following distribution of pathogenic organisms: pneumococcus, 95.65 per cent; hemolytic streptococcus, 3.8 per cent; Friedländer's bacillus, 0.4 per cent; influenza bacillus, 0.05 per cent, and *Staphylococcus aureus*, 0.1 per cent.

The incidence of the various types of pneumococcus was as follows: pneumococcus type I, 33.6 per cent; pneumococcus type II, 19.2 per cent; pneumococcus type III, 13.4 per cent; pneumococcus type IV, 33.1 per cent. There was considerable variation from year to year in the incidence of the various types.

A study of the relation of types to age shows that young people are particularly prone to pneumococcus type I infections, and elderly people to pneumococcus type III. Type II and type IV show no special predilection for any age group.

A study of the incidence of type in relation to sex shows that type I and type II are commoner in men than in women. Type III and type IV are commoner in women than in men. Type III is almost twice as common in women as in men. Type I pneumonia is three times as common in men under 50 as it is in women over 50. On the other hand, type III pneumonia is more than three times as common in women over 50 as it is in men under 50.

The percentage of mixed infections among the cases of pneumococcic pneumonia is lowest in type I cases (18.4 per cent) and highest in the type IV group (31.2 per cent). The incidence of mixed infections varies from year to year, being highest during years when influenza is prevalent. By far the commonest mixed infection was that of the pneumococcus in association with the influenza bacillus. The pneumococcus and hemolytic streptococcus is the next most frequent combination.

The incidence of preexisting systemic disease is highest in the pneumococcus type III group, 63.3 per cent of all type III infections occurring in patients with systemic disease.

The type of pneumococcus appears to bear no relation to the lobe involved or to the extent of the infection. Three and four lobe

8. Cecil, R. L., and Larsen, J. P.: Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, J. A. M. A. **79**:343 (July 29) 1922. Cecil, R. L., and Baldwin, H. S.: The Treatment of Lobar Pneumonia with Subcutaneous Injections of Pneumonoccus Antibody Solution, J. Pharmacol. & Exper. Therp. **24**:1, 1924.

infections are as relatively frequent in the milder types (I and IV) as in the severe types (II and III).

Twenty-four per cent of the cases of pneumococcic pneumonia showed pneumococci in the blood. The incidence of bacteremia is higher in the severe types (II and III) than in the mild types (I and IV). Type II is essentially the pneumococcus of bacteremia, yielding positive blood cultures in 39.7 per cent of the cases.

No striking differences in the clinical course could be demonstrated as characteristic of the various types of pneumococci. The average duration of the disease for the various types ranged from 8.6 to 9.1 days, type III running the longest course. Type III infections also run the longest course in monkeys.

A study of the mode of termination in the cases of pneumococcic pneumonia in which the patients recovered showed that 49.6 per cent terminated by crisis. Crisis was most frequent in type I infections, 56.6 per cent; type II, 50 per cent; type III, 39.3 per cent; type IV, 45.5 per cent.

The death rates for the various types (without specific treatment) were as follows: type I, 20.7 per cent; type II, 42 per cent; type III, 41.6 per cent; type IV, 29.2 per cent. Types I and IV are the milder forms, types II and III are the severe forms, of pneumococcic pneumonia.

A study of the death rate in relation to age shows a steadily increasing death rate for each decade. In patients under 20, the death rate for all types was 11.1 per cent; in those over 60, the death rate was 52.7 per cent. Age is probably the most important single factor in determining the death rate in pneumonia. Pneumococcus type I pneumonia has a low death rate, presumably because it is the pneumonia of young people. Pneumococcus type 3 pneumonia has a high death rate, chiefly because of its prevalence in elderly people. In patients under 30, type III pneumonia is not a severe infection.

The relation of bacteremia to death rate was striking in all four types. Among 240 patients whose blood remained sterile, the death rate was only 18.7 per cent; among eighty-nine patients whose blood cultures were positive, the death rate was 83.1 per cent.

The association of some systemic disease with pneumonia increases the death rate. Among patients free from systemic disease, the death rate was 23.4 per cent; among those with systemic disease, the death rate was 46.4 per cent.

In all four types of pneumonia the death rate was definitely related to the number of lobes involved; for single lobe infections it was 20.9 per cent; two lobes, 36.3 per cent; three lobes, 40.8 per cent, and four lobes, 65.5 per cent.

Some form of pneumococcic complication occurred in 12.1 per cent of type I cases. The incidence of pneumococcic complications was almost twice as high for type I infections as for the other three types.

Empyema was the commonest complication, occurring in 5.1 per cent of all cases. The incidence of empyema was considerably higher in type I infections than in any of the other types. Empyema is a much more serious complication when it develops during the active stage of pneumonia than when it occurs after the crisis.

THE CORONARY CIRCULATION *

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Experimental ligation of the coronary arteries [1] and observations on man following the occlusion of these vessels [2] have demonstrated that the heart is extremely sensitive to a reduction in its blood supply. It would seem that a knowledge of the factors concerned in the regulation of the coronary circulation is important for a better understanding of impaired cardiac function. It is possible that a further study of this subject may furnish an explanation for the cause of cardiac failure in certain instances which are at present obscure and may perhaps suggest a more satisfactory means of treatment. The present report is concerned with studies of certain features of the coronary circulation in which the author has been interested during the last three years.

INFLUENCE OF THE VAGI AND SYMPATHETIC NERVES ON THE CORONARY ARTERIES

The action of the vagi and sympathetic nerves on the coronary arteries has been more extensively investigated perhaps than any other physiologic aspect of the coronary circulation. It has been approached through the study of short sections of the coronary arteries suspended in Ringer's solution and through observation on the isolated and the intact heart and heart-lung preparation.

The studies on isolated sections of the coronary arteries have been concerned chiefly with observations on the effect of epinephrine because of the action that this drug is said to have on the sympathetic nerve.[3] By this method epinephrine has repeatedly produced a dilatation of strips of coronary arteries from the sheep, goat, ox, calf and rabbit.

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* Read before the Portland Academy of Medicine, Portland, Oregon, Oct. 13, 1926.

1. Miller and Mathews: Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch. Int. Med. **3**:476 (June) 1909. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, ibid. **22**:8 (July) 1918.

2. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912; Thrombosis of Coronary Arteries, ibid. **72**:387 (Feb. 8) 1919.

3. Lagendorff: Zentralbl. f. Physiol. **21**:551, 1907. Cow: J. Physiol. **42**: 125, 1911. Eppinger and Hess: Ztschr. f. exper. Path. u. Therap. **5**:622, 1909. Barbour: J. Exper. Med. **15**:404, 1912. Park: ibid. **17**:532, 1912. Ishihara: Fuknoka-Ilwadaigaku-Zasshi. **14**:3, 1921.

Barbour,[4] however, who used human coronary arteries removed at autopsy while the body was still warm, observed a constriction; but in a similar series of experiments, he noted a dilatation when the coronary arteries of the calf, sheep and pig were employed. Cow [5] reported that the strips taken from different sections of the same artery varied in their response to epinephrine. While this method of investigation has yielded certain important information, it is subject to criticism because of the obviously abnormal state under which these vessels were studied. Furthermore, since the smaller arteries and the capillaries, in many instances, are known to react in a different manner from the larger vessels,[6] observations made on the isolated ring preparations cannot be applied to the whole coronary system without reservations.

In the studies on the isolated heart the perfusion fluid was introduced through a cannula inserted into the aorta or into the coronary arteries. Wiggers [7] has pointed out a possible source of error in determining the rate of coronary flow by perfusion of the heart through a cannula inserted into the aorta because of the possible imperfect closure of the aortic valves allowing a leakage of fluid into the left ventricle. He eliminated this source of error by introducing the cannulas directly into the coronary arteries.

My co-workers and I [8] have recently investigated the question of the leakage of the aortic valves. In some experiments the inferior and superior vena cava were ligated and a cannula introduced into the pulmonary artery. The return of the perfusion fluid to the right side of the heart was thus separated from any that might leak past the aortic valves or return directly to the left ventricle from the coronary circulation. The same feature was further studied by the ligation of the pulmonary veins and by the insertion of a cannula into the tip of the left auricle. In both instances the amount of perfusion fluid which escaped from the left ventricle was negligible.

The rate of coronary flow in the perfused heart has usually been determined by measuring the fluid which escapes from the right auricle. In a series of experiments performed by my co-workers and me, the perfusion fluid escaping from the right auricle has been directed by a funnel into a tipping bucket, the emptying of which is automatically registered on a kymograph. Brodie and Cullis [9] devised an ingenious plethysmograph by means of which a constant record of the coronary

4. Barbour (footnote 3, fourth reference).
5. Cow (footnote 3, second reference).
6. Krogh; J. Physiol. **53**:399, 1919-1920; ibid. **55**:412, 1921; The Anatomy and Physiology of Capillaries, Yale University, New Haven, 1922.
7. Wiggers: Am. J. Physiol. **24**:391, 1909.
8. Smith, Miller and Graber: J. Clin. Investigation **2**:157, 1925.
9. Brodie and Cullis: J. Physiol. **43**:313, 1911-1912.

outflow was obtained. Sassa,[10] and Drury and Sumbal [11] have employed the method introduced by Atzler and Frank [12] for measuring the coronary inflow. The latter method is perhaps the most delicate means of registration, but is dependent on a closed system which somewhat restricts its field of application.

In the intact heart the rate of coronary flow has been estimated by measuring the blood permitted to escape through a cut in a coronary vein.[7] More recently the Morowitz and Zahn cannula,[13] which is introduced into the coronary sinus, has been employed.[14] This cannula has also been used in the heart-lung preparation.[15] It affords an accurate means of studying the rate of coronary flow. While not all the blood returns to the right side of the heart through the coronary sinus, this amount has been found by Starling to represent a fairly constant proportion of the total coronary flow under varying conditions.

Epinephrine has likewise been employed in the study of the coronary circulation of the isolated [16] and intact heart [17] and in the heart-lung preparation [18] by observing the effect of the drug on the rate of coronary flow. In most instances the rate of flow was increased. The dose of the drug employed was usually sufficient to produce a striking accelerating action on the heart. Brodie and Cullis [9] avoided the marked stimulating effects of epinephrine by reducing the size of the dose. In those instances in which minute quantities were employed, a decrease in the rate of perfusion was observed. As the size of the dose was increased, causing the stimulating action to become more marked, the decrease in the rate of coronary flow was replaced by augmentation.

Recently Drury and Smith,[19] by means of the microscope, studied the effects of epinephrine applied locally to the coronary arteries of the tortoise. In all instances the vessels under observation were constricted. Sometimes the lumen was entirely obliterated. After the vessels were constricted by epinephrine, they were dilated to their

10. Sassa: Arch. f. d. ges. Physiol. **198**:543, 1923.
11. Drury and Sumbal: Heart. **10**:267, 1924.
12. Atzler and Frank: Arch. f. d. ges. Physiol. **181**:144, 1920.
13. Morowitz and Zahn: Zentralbl. f. Physiol. **26**:465, 1912; Deutsches. Arch. f. klin. Med. **116**:364, 1914.
14. Sassa (footnote 10). Smith, Miller and Graber: Relative Importance of Systolic and Diastolic Blood Pressure in Maintaining Coronary Circulation, Arch. Int. Med. **38**:109 (July) 1926.
15. Markwalder and Starling: J. Physiol. **47**:275, 1913-1914. Nakagawa: J. Physiol. **56**:340, 1922. Anrep: Physiol. Rev. **6**:596, 1926.
16. Barbour and Prince: J. Exper. Med. **21**:330, 1915. Bond: ibid. **12**:575, 1910. Schafer: Zentralbl. f. Physiol. **19**:218, 1905-1906. Wiggers (footnote 7).
17. Meyer: Arch. f. Anat. u. Physiol. 1912, p. 223. Morowitz and Zahn (footnote 13). Wiggers (footnote 7).
18. Markwalder and Starling (footnote 15, first reference).
19. Drury and Smith: Heart **11**:71, 1924.

original size by faradic stimulation of the vagus. This dilating action of the vagus was readily eliminated by atropine. Drury and Sumbal [11] later noted a striking decrease in the rate of the coronary flow in the heart of a tortoise after the introduction of epinephrine into the perfusion fluid. In the same series of experiments similar results were obtained by the stimulation of the sympathetic nerves. In further observations on the coronary arteries of the tortoise, Sumbal [20] studied the effects of acetylcholine by direct application and perfusion methods. When the drug was applied locally to the coronary artery, a dilatation was noted, and when it was introduced into the perfusion fluid, an increase in the rate of coronary flow followed.

I [21] have more recently studied the effect of epinephine and acetylcholine on the coronary flow in the perfused heart of the rabbit. Epinephrine in dilutions of approximately 1 : 200,000,000 was employed to avoid the complicating effects produced by the extreme cardiac stimulation resulting from the higher concentrations ordinarily used. Epinephrine in this dilution produced a decrease in the rate of the coronary flow varying from 12 to 22 per cent. The diminished perfusion rate began immediately after the introduction of the drug and persisted up to the point of greatest cardiac stimulation. At this point the coronary flow was usually slightly augmented for a short time. Even with these minute doses of epinephrine, there was a distinct stimulating effect on the heart as indicated by the acceleration in rate and increase in the amplitude of contraction. These results demonstrate that epinephrine constricts the coronary arteries of the rabbit when the dose employed is sufficiently small to avoid the extreme cardiac stimulation. When larger concentrations were used, the decrease in the rate of coronary flow was replaced by an augmentation. It is believed that the increase in the rate of coronary flow heretofore reported may be attributed to the extreme stimulating action on the heart by the dose employed.

Acetylcholine is generally regarded as having an inhibitory action on the heart comparable to that produced by stimulation of the vagus.[22] In the aforementioned investigation acetylcholine was introduced into the coronary arteries in dilutions varying from 1 :100,000 to 1 :200,000. The drug in these concentrations greatly reduced the heart rate, and in some instances produced cardiac standstill. Coincident with the reduction in the rate, the amplitude of contraction was diminished. With the onset of these changes, the perfusion rate was greatly augmented. The introduction of atropine into the perfusion fluid in a concentration of

20. Sumbal: Heart **11**:285, 1924.
21. Smith, Miller and Graber: Am. J. Physiol. **77**:1, 1926
22. Hunt and DeM. Taveau: Brit. M. J. **2**:1788, 1906. Dale: J. Pharmacol. & Exper. Therap. **6**:147, 1914. Hunt: Am. J. Physiol. **45**:197, 1918.

1:20,000 prevented or eliminated these effects. The results were thus similar to those observed by others in the study of the action of acetylcholine on the coronary artery of the tortoise [20] and on other arteries in the mammal.[23]

The results of stimulation of the sympathetic and of the vagus nerves of the mammal have varied in the hands of different investigators. Morowitz and Zahn [13] observed an increase in the rate of coronary flow during sympathetic stimulation. In these experiments neither the cardiac rate nor the blood pressure was controlled. Wiggers [7] reported a decreased flow from a wounded coronary vein during the stimulation of the vagosympathetic nerves of the dog after atropinization. Nakagawa [24] noted no change in the rate of coronary flow in the heart-lung preparation during vagal stimulation. Sassa [19] studied the coronary flow by cannulizing the coronary arteries in the intact and isolated heart of the cat and measured the rate of inflow by the Atzler and Frank method. A decrease in the rate of flow was usually recorded at the beginning of sympathetic stimulation even with increased cardiac rate, whereas on vagal stimulation there was an initial increase in the rate of inflow associated with a reduction in the cardiac rate.

The question as to whether the vagi and sympathetic nerves provide the coronary arteries with a vasomotor mechanism has been difficult to answer. It is not surprising that the results from the use of epinephrine and electrical stimulation of the nerves have varied because of the difficulty in controlling of the various factors which influence the coronary circulation. The contraction of the heart opposes either a dilatation or a constriction of the coronary arteries. The opposition from this factor is conceived to be great in the mammalian heart because of the rapid rate of contraction. This feature is well illustrated by the action of epinephrine on the isolated or intact heart when the dose is sufficient to produce a marked stimulating effect. It is perhaps reduced to the minimum in the slowly beating heart of the tortoise. Even here it was difficult to obtain the constricting effect of epinephrine on the surface vessels after the cardiac rate was accelerated by the stimulating effect of the drug.[19] Furthermore, the blood pressure is perhaps the greatest factor in maintaining the coronary circulation. This has not always been controlled. Then, too, the vagi and the sympathetic nerves are apt not to be clearly separated in the mammal, particularly in the dog, in which the main trunk of the vagus is said to contain sympathetic fibers. The possibility of stimulating both nerves when intending to stimulate only one cannot be entirely disregarded. At present it would seem that there is no doubt regarding the action of the vagi and sympathetic nerves on the coronary artery of the tortoise. The

23. Hunt (footnote 22, third reference).
24. Nakagawa (footnote 15, second reference).

evidence that these nerves may provide the coronary arteries of the mammal with a similar vasomotor mechanism is suggestive but not conclusive.

THE INFLUENCE OF BLOOD PRESSURE

The susceptibility of the heart to changes in the aortic pressure was early recognized in perfusion experiments. Herlitzka [25] observed that the perfused heart of the rabbit ceased to beat when the pressure of the perfusion fluid was reduced below from 13 to 18 mm. of mercury. If, however, the pressure was gradually increased, the cardiac contractions appeared in periodic groups. After further increase in pressure, the action of the heart became more regular with alternating strong and weak beats which were later replaced by contractions of equal strength. Langendorff [26] and Porter [27] noted that an increase in perfusion pressure greatly augmented the rate of coronary flow. The influence of blood pressure on the coronary flow was perhaps best appreciated following the observations of Markwalder and Starling.[18] In some instances they obtained 100 per cent increase in the rate of coronary flow by elevating the blood pressure from 80 to 100 mm. of mercury. Morawitz and Zahn [13] and De Barenne [28] have since observed a similar dependence of the coronary flow on the arterial pressure.

Recently I [29] studied the relative importance of the systolic and diastolic pressure in maintaining the coronary circulation. Dogs were employed in this series of experiments. The blood pressure was recorded on the kymograph by a Straub membrane manometer. This instrument was employed in order to obtain a more accurate record of the systolic and diastolic pressures. The rate of coronary flow was determined by means of the Morowitz-Zahn cannula. The blood from the coronary sinus was maintained at a constant temperature and reintroduced into the femoral vein. Changes in the blood pressure were produced by constricting the thoracic aorta with an adjustable clamp and by the experimental production of arteriovenous aneurysm and aortic regurgitation.

In those experiments in which the thoracic aorta was constricted by an adjustable clamp, it was possible, within certain limits, to increase the diastolic pressure without altering the systolic pressure. In each instance there was a striking increase in the rate of coronary flow associated with the elevation of the diastolic pressure, even in those experiments in which the systolic pressure was slightly reduced.

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25. Herlitzka: Tigerstadt Physiologie des Kreislaufes, Berlin, 1921, vol. 1, p. 319.
26. Langendorff: Arch. f. d. ges. Physiol. **78**:423, 1899.
27. Porter: Am. J. Physiol. **1**:141, 1898.
28. De Barenne: Arch. f. d. ges. Physiol. **177**:217, 1919.
29. Smith, Miller and Graber (footnote 14, second reference).

When the arteriovenous aneurysm was employed, the diastolic pressure was reduced and the systolic increased. In these experiments there was a definite decrease in the rate of coronary flow in spite of the increase in the systolic pressure. In the experiments in which an aortic regurgitation was produced by puncturing the aortic valves, the results were similar to those of the arteriovenous aneurysm. The systolic pressure was increased, the diastolic decreased, and there were corresponding changes in the coronary flow. The alterations in the blood pressure and the changes in the coronary flow varied with the extent to which the aortic valves were damaged. In one typical experiment during the control period the systolic pressure was 100 and the diastolic 50. The rate of flow from the coronary sinus was 240 cc. a minute. Following the puncture of one valve the systolic pressure was increased to 120 and the diastolic fell to 30. The flow from the coronary sinus was reduced to 195 cc. a minute. Later the same valve cusp was torn loose from its base. Following this procedure the systolic pressure at once increased to 150 and the diastolic fell to 15. The flow from the coronary sinus was further reduced to 150 cc. a minute.

The results of this series of experiments show that the rate of coronary flow is greatly altered by a change in the diastolic pressure even in the presence of changes in the systolic pressure in the opposite direction. In one instance in which there was a reduction of only 5 mm. of mercury in the diastolic pressure associated with an increase of 10 in the systolic pressure, there was a decrease in the flow of the blood from the coronary sinus from 277 to 250 cc. a minute. Similarly in those experiments in which there was a corresponding elevation of the diastolic pressure, even though the systolic pressure remained constant or was even slightly reduced, there was a comparable increase in the rate of coronary flow. It would seem from these results that the maintenance of an efficient coronary circulation is fundamentally dependent on the height of the diastolic pressure. While the systolic blood pressure no doubt influences the coronary flow, it is subordinate to that of the diastolic pressure.

On the basis of these observations it is suggested that the decreased coronary flow associated with the diminished diastolic pressure in aortic regurgitation and arteriovenous aneurysm is probably a significant factor in the development of the cardiac hypertrophy and later cardiac failure.

INFLUENCE OF THE CARDIAC RATE

Porter [27] observed a decrease in the rate of coronary flow in the perfused heart of the cat when the cardiac rate was slowed by vagal stimulation. He concluded that the volume of blood passing through the coronary vessels was influenced by the heart rate. The effect of variations in the cardiac rate on the coronary circulation has since been

studied by Morawitz and Zahn,[13] Nakagawa,[24] Sassa,[10] Miyaka,[30] Anrep and Segall [31] and Hammouda and Kinoseta.[32] Nakagawa employing the heart-lung preparation and Sassa in studies on the isolated heart produced changes in the heart rate by altering the temperature of the blood or perfusion fluid. In both series of experiments the reduction and the acceleration in the cardiac rate, induced respectively by cooling and heating of the blood or perfusion fluid, produced within certain limits a corresponding increase and decrease in the rate of coronary flow. Both of these investigators appreciated that the changes in the coronary flow induced in this manner could not be entirely attributed to changes in the cardiac rate; they therefore resorted to other means of changing the rate. Nakagawa, in his further experiments, accelerated the heart rate by induced shocks to the sinus node and slowed the heart by vagal stimulation. In this study, no appreciable change was noted in the rate of coronary flow. In his subsequent studies, Sassa, induced changes in the cardiac rate by cooling and warming the sinus node by means of a water thermode. He observed a decrease in the coronary flow when the cardiac rate was reduced. In those instances, however, in which heat was applied to the sinus node associated with an acceleration in cardiac rate there was little increase in coronary flow.

Observations on the effects of changes in the cardiac rate produced by warming and cooling the sinus node have since been made by Miyaka, and no alteration in the coronary flow has been observed. Anrep and Segall, working with the heart-lung preparation, did not note any change in the volume of the coronary flow by driving the heart at varying rates from 60 to 200 a minute. These observers cite the work of Hammouda and Kinosita on the isolated heart as confirming their results.

My co-workers and I [33] have recently investigated the influence of cardiac rate on coronary flow. The subject was approached by studies on the isolated and on the intact heart. In the former the heart of the rabbit was driven at different rates by means of rhythmical induced shock. In every instance an increase in heart rate was associated with an augmentation of the coronary flow. In general the increase in coronary flow seemed to depend on the initial cardiac rate and the extent to which the heart was accelerated. The greatest increase in the rate of coronary circulation was observed in those instances in which the initial cardiac rate was about 120 and the acceleration more than 50 beats a minute. A further increase in the cardiac rate above 200 a minute usually did not produce significant changes in the coronary flow. Fur-

30. Miyaka, quoted by Anrep (footnote 15, third reference).
31. Anrep (footnote 15, third reference).
32. Hammouda and Kinosita, quoted by Anrep (footnote 15, third reference).
33. Smith, Miller and Graber: Unpublished work.

thermore, in those experiments in which the initial heart rate was above 160 a minute, further acceleration was not associated with changes in the coronary flow comparable to that produced in a heart with a lower initial rate.

Further studies were made on the intact heart of the dog in which changes in the cardiac rate were produced by heating and cooling the sinus node and by vagal stimulation. In all instances a constant blood pressure was maintained. By means of the application of heat and cold to the sinus node, it was possible to produce changes in the cardiac rate ranging from 30 to 60 beats a minute. This decrease and increase in heart rate, respectively, was associated with a sudden reduction and augmentation of the coronary flow. In those experiments in which the cardiac rate was decreased by vagal stimulation, the reduction in the rate of coronary circulation was striking.

It is concluded from these results that reduction and acceleration of the cardiac rates within certain limits are associated with definite changes in the rate of coronary flow. The most striking alterations in the coronary circulation were observed during the changes from the slow beat induced by vagal stimulation to the accelerated rate produced by warming the sinus node.

THE INFLUENCE OF CARDIAC IRREGULARITIES

The coronary circulation has been studied during ventricular fibrillation. Anrep, in his recent review,[31] mentions an investigation in which he, with Downing, Cruickshank and Subba Rau studied the time relations between the changes in the coronary outflow and inflow and the different phases of the cardiac cycle in the heart-lung preparation. In this work observations were made on the influence of heart block, premature contraction and auricular and ventricular fibrillation. No definite statement, however, was made concerning the influence of these various types of abnormal cardiac mechanism on the rate of coronary flow, and a detailed report of these experiments is not available. To my knowledge, there has been no other observation concerning the influence of the clinical types of cardiac irregularities on the coronary circulation.

This subject is being investigated on the intact heart of the dog and will be discussed more in detail in a future report. So far, premature contraction induced by electrical stimulation of the auricles and ventricles has not produced any significant change in the rate of coronary flow. The effects of auricular fibrillation produced by faradic stimulation of the auricles have varied. In most instances there has been a definite increase in the rate of coronary flow. In one experiment, however, in which the auricular fibrillation appeared spontaneously and lasted for several minutes, there was practically no change in the rate of coronary flow after the establishment of a normal cardiac mechanism. In another

experiment, in which the faradic stimulation of the auricles was followed on several occasions by the onset of a rapid and seemingly regular cardiac action, there was no significant change in the rate of flow from the coronary sinus.

A slow cardiac rate comparable to that accompanying complete heart block was produced by vagal stimulation. In each of these experiments there was a striking reduction in the rate of coronary flow.

THE INFLUENCE OF CAFFEINE, THEOBROMINE AND THEOPHYLLINE

Caffeine, theobromine and theophylline are invariably mentioned in the discussion of the treatment of patients with cardiac failure. One explanation of their beneficial effect has been sought through their possible action on the coronary arteries. The results of the investigation of the action of these drugs on the coronary arteries have varied considerably with the different observers. Hedbom [34] obtained an increase in the rate of coronary flow in the perfused heart with caffeine in concentration of 1:20,000. Loeb,[35] on the other hand, observed little increase in the coronary output following the administration of caffeine, whereas theobromine greatly augmented the rate of perfusion. Heathcot [36] studied the action of caffeine, theobromine and theophylline in concentration varying from 1:2,000 to 1:40,000. He obtained a marked increase in rate of coronary flow with the higher concentration. When, however, these drugs were employed in dilutions of 1:20,000 and 1:40,000, caffeine and theobromine produced little if any change, and theophylline produced from 20 to 30 per cent increase. Sakai and Saneyoshi [37] investigated the effect of caffeine sodiobenzoate and theobromine sodiosalicylate on the coronary flow of the intact heart of the cat, employing the Morowitz-Zahn cannula in their experiments. They concluded that the slight increase in the coronary output which they observed following the injection of caffeine sodiobenzoate could satisfactorily be explained on the basis of the elevation in blood pressure. Small doses of theobromine sodiosalicylate produced slight increase in the coronary flow, whereas when large doses were introduced, there was a drop in the blood pressure associated with a marked augmentation of the flow through the coronary arteries. Guggenheimer and Sassa [38] studied the action of caffeine, theophylline and euphyllin on the coronary arteries of the isolated heart of the cat. Caffeine in dilutions of 1:25,000 increased the rate of coronary flow 41 per cent. Theophylline and euphyllin in similar concentrations produced a 40 and 80 per cent

34. Hedbom: Skandin. Arch. f. Physiol. **9**:1, 1899.
35. Loeb: Arch f. exper. Path. u. Pharmakol. **51**:64, 1903-1904.
36. Heathcot: J. Pharmacol. & Exper. Therap. **16**:327, 1920.
37. Sakai and Saneyoshi: Arch. f. exper. Path. u. Pharmakol. **78**:331, 1914-1915.
38. Guggenheimer and Sassa: Klin. Wchnschr. **2**:1451, 1923.

increase, respectively. These investigators attributed the change in the rate of the flow of the perfusion fluid after caffeine and theophylline to the acceleration of the cardiac rate, and pointed out that euphyllin did not elevate the heart rate more than 10 per cent. The latter preparation was thus recommended therapeutically in coronary disease because of its marked dilating action.

We have compared the action of euphyllin with that of caffeine sodiobenzoate, theobromine sodiosalicylate and theophylline in experiments on the isolated heart of the rabbit in which the cardiac rate was controlled. Caffeine sodiobenzoate in concentrations of 1:25,000 solution had little if any effect on the cardiac rate amplitude of contraction and coronary flow. Theobromine sodiosalicylate in dilutions of 1:25,000 in most instances produced no change or even decreased the coronary flow. When the concentration of 1:50,000 was used, the rate of flow was slightly accelerated. Theobromine sodiosalicylate in either of these concentrations apparently had no effect on the cardiac rate. In some instances the amplitude of contraction was diminished and associated with some increase in tone.

Theophylline in concentrations of 11:25,000 and 1:50,000 increased the rate of coronary flow from 20 to 45 per cent. The acceleration of the cardiac rate was not a prominent feature. The greatest increase in coronary flow was produced by the drug when there was no change in the cardiac rate.

Euphyllin in concentrations of 1:25,000 and 1:50,000 increased the rate of perfusion from 40 to 90 per cent. It had a somewhat greater tendency to accelerate the cardiac rate than did theophylline. With both drugs, however, the increase in coronary output was independent of the accelerating action on the heart, as was indicated by experiments in which uniform cardiac rate was maintained by rhythmical stimulation.

The variations in the results obtained in the investigations of the action of caffeine, theobromine and theophylline on the coronary arteries have apparently been due to the difference in the concentration of the drug employed. The concentrations employed in our experiments were similar to those used by Guggenheimer and Sassa and estimated to approximate the therapeutic dose in man. In those instances in which higher concentrations were employed, particularly as 1:2,000, the results obtained were probably due to the toxic action of the drug on the heart.

BASAL METABOLISM IN VITAMIN B STARVATION*

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The basal metabolism in vitamin B starvation has been much discussed by various workers in recent years. The earliest article now available to us is that of Caspari and Moszkowski.[1] After practical experience during research in New Guinea, Moszkowski concluded that the so-called beriberi of man is a disease of metabolism essentially due to the ingestion of polished rice, a view which was contradicted by other workers. To verify this opinion, Moszkowski offered to make experiments on himself. He was kept under observation by Caspari and others. About a month after the beginning of the rice diet, clinical symptoms began to appear, which eventually became significant. The chief symptoms were: general wandering neuralgia, tenderness of the muscles and skin, especially of the calf muscles, Lasègue's symptom, paresthesia and numbness of the hands and feet, weakness and somnolence, a sense of restriction in the chest, lability of the pulse, edema of the feet, painful effusion of the tendon sheaths, especially of the hands and ankles, and looseness of the knees. The heart was slightly enlarged to the right and markedly to the left, extending 2 cm. beyond the nipple line; this can be accounted for in part by the marked elevation of the diaphragm. The sounds were dull everywhere, the first sound at the apex being distinctly impure; the second pulmonic sound was accentuated. The motor nerve did not show any direct reaction of degeneration; the knee and achilles reflexes were active.

The clinical symptoms other than those of the heart were similar to those of the enterotoxic polyneuritis of von Noorden, especially as during the course of the disease there was a severe membranous enteritis, which is the chief clinical symptom in von Noorden's disease. A consideration of all the symptoms, especially those of the heart, and their prompt amelioration by the administration of the extract of rice bran, led the observers to conclude that this was a case of beriberi.

In the course of the research, Caspari and his associates found that the consumption of oxygen and the body weight diminished steadily. This was true, however, only during the first period of the research.

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1. Caspari, W., and Moszkowski, M.: Weiteres zur Beriberi-Frage, Berl. klin. Wchnschr. **50**:1515, 1913.

Later a distinct increase was observed in the consumption of oxygen. An increase in the basal metabolism is known to occur only as the result of some irritation or intoxication. To the first mechanism belongs also the product of internal secretion, such as that of the sexual and thyroid glands. Research work on respiration has shown that a toxic or irritating substance may exist in an organism. On the other hand, when experimenters fed pigeons with eggs of the domestic fowl, salts and grape sugar for more than a month, the animals showed an increase in weight and were healthy. They then added a sufficient amount of polished rice to this diet, and found that within varying periods polyneuritis developed. They concluded from the foregoing experiments that the development of beriberi does not depend on deficiency in nutrition but on the presence of a toxic substance, that is, on an intoxication.

Ramoino [2] found that by feeding pigeons exclusively with polished rice a rapid decrease of the respiratory quotient occurred, but that it soon became normal when an extract prepared from rice bran was given. He attributed this phenomenon to the lack of vitamin which has a catalytic action, and consequently to insufficient oxidation of the nutritive substances. The accumulation of the intermediate catabolic products has an intoxicating effect on the tissues and causes the characteristic symptoms. A review of Ramoino's protocols shows that the body weight and consumption of oxygen of animals fed on polished rice were simultaneously reduced. The decrease in consumption of oxygen was in some cases nearly parallel with the decrease in body weight, while in others it was more marked.

Abderhalden [3] and his co-workers made an extraordinary series of observations on the gas exchange of the entire animal as well as of isolated cells and tissues of pigeons suffering from alimentary dystrophy, and found that the gas exchange in both was markedly diminished. The foodstuffs which prevent the appearance of the well known symptoms after a diet consisting exclusively of polished rice, or which cause them to disappear, also cause cell respiration to be increased. For example, in pigeons that were fed exclusively on polished rice and showed lowered temperature and decreased gas exchange, the gas exchange increased promptly and the temperature became normal when a small amount of foodstuffs prepared from yeast or rice bran was

2. Ramoino, P.: Contributo allo studio delle alimentazioni incomplete. Pathologica **7**:101, 1915.

3. Abderhalden, E., and Schmidt, L.: Weitere Beiträge zur Kenntnis von organischen Nahrungsstoffen mit spezifischer Wirkung; III. Mitteil., Pflüger's Arch. f. d. ges. Physiol. **185**:141, 1920. Abderhalden, E.: IV. Mitteil., ibid. **187**: 80, 1921; V. Mitteil., ibid. **188**:60, 1921. Abderhalden, E., and Wertheimer, E.: VII. Mitteil., ibid. **191**:258, 1921. Abderhalden, E.: VIII. Mitteil., ibid. **191**: 278, 1921; IX. Mitteil., ibid. **192**:163, 1921. Abderhalden, E., and Wertheimer, E.: X. Mitteil., ibid. **192**:174, 1921; XIII. Mitteil., ibid. **194**:647, 1922; XVII. Mitteil., ibid. **195**:460, 1922.

administered. The cells and tissues of pigeons which suffered from alimentary dystrophy, and which showed a decrease in respiration, showed an immediate increase in the consumption of oxygen when the aforementioned foodstuffs were added to the diet. From all these observations, it was concluded that on a diet consisting exclusively of polished rice, the cell respiration becomes poor, and oxidation is restricted. Respiration also becomes longer and deeper in pigeons fed on rice. Further research also confirmed the observation that pigeons fed on rice show an increased sensibility to deficiency in oxygen and increase in carbon dioxide.

Hess and Messerle [4] made investigations concerning the respiratory power of various tissues of pigeons diseased from feeding on rice, and compared it with that of healthy pigeons. The diseased pigeons showed a marked insufficiency of respiration in various tissues, especially in the brain.

Anderson and Kulp [5] found that in poultry fed exclusively on polished rice there was a lowering of the basal metabolism and a decrease in the consumption of food with loss in weight, and that in from thirty-eight to forty-four days symptoms of paralysis appeared. They observed that the heat production of chickens, when calculated on the basis of kilograms of weight, decreased from 3 calories during usual nourishment to about 2.25 calories per kilogram per hour during vitamin starvation and polyneuritis. A single administration of yeast extract not only relieved the symptoms of polyneuritis, but also started an extremely active metabolism. During the first two or three weeks after recovery, the consumption of food was small, and there was little gain in weight. The heat production of the emaciated organism, however, was equal to that of the well nourished animal. These authors found almost no difference in the value of the respiratory quotient during vitamin starvation and during normal basal metabolism; this agrees with the results of Janson and Mangkoewinoto, but which differs from those reported by Ramoino.

Kinoshita [6] found that giving pigeons food deficient in vitamin B caused a marked diminution of the respiratory quotient during the later period of incubation and especially after the appearance of polyneuritis. The consumption of oxygen increased, however, especially during the last stages of the disease as compared with that of the period of incubation.

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4. Hess, W. R.: Die Rolle der Vitamine im Zellmechanismus, Ztschr. f. phys. Chem. **117**:284, 1921. Hess, W. R., and Messerle, N.: Untersuchungen über die Gewebeatmung bei Avitaminose, ibid. **119**:176, 1922.

5. Anderson, R. J., and Kulp, W. L.: A Study of the Metabolism and Respiratory Exchange in Poultry During Vitamin Starvation and Polyneuritis, J. Biol. Chem. **52**:69, 1922.

6. Kinoshita, R.: Ueber den Gaswechsel bei der Reiskrankheit des Geflügers, Tr. Japanese Path. Soc. **12**:186, 1922.

From this observation he considered that the ingredients which are oxidized as the source of energy in the body of pigeons fed on rice must be other than carbohydrate, although this is administered in sufficient amount. This fact proves the opinion of Ogata and his co-workers that the vital point of the rice disease is a disturbance of the metabolism of carbohydrate as the result of vitamin B deficiency.

We [7] made an investigation in persons with mild cases of beriberi in which the basal metabolism was normal or nearly normal, as well as in healthy men, to determine whether any change occurs in the basal metabolism or in the variation in the respiratory exchange during vitamin B starvation. The main part of the diet consisted of well polished and thoroughly washed rice, and the additional foods were free from vitamins but contained enough protein, fat and salts. The basal metabolism decreased during vitamin B starvation and rapidly became normal after the administration of vitamin B preparations. In vitamin B starvation we often found loss of appetite and decrease in consumption of food, but the lowering in the basal metabolism occurred before there was a change in appetite, consumption of food or body weight. On account of the respiratory quotient, we could not find any definite change in metabolism during the course of vitamin B starvation, although it seemed somewhat likely to become lower.

Groebbels [8] determined the consumption of oxygen in white mice fed with polished rice. He found that the increase in the consumption of oxygen and body weight during the first period of vitamin starvation was accompanied by a decrease in both during the following period. He called these two periods the avitaminosis period and the starvation period. He attributed the former to insufficiency of vitamin and the latter, not directly to avitaminosis, but to the secondary disturbance of metabolism of protein and salts following vitamin starvation.

Knipping and Kowitz [9] made an experiment on human subjects suffering from scurvy by administering food autoclaved three hours at 130 C. They found a marked increase in the basal metabolism when the food contained vitamins. After the administration of vitamin preparations, a diminution of metabolism was observed in all cases.

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7. Okada, S.; Sakurai, E.; Ibuki, T., and Kabeshima, H.: On the Basal Metabolism in Vitamin B Starvation and in Beriberi, Ikai Jiho no. 1479 (Nov. 4) 1922; Japan M. World. **3**:102 (May 15) 1923.

8. Groebbels, F.: Studien über das Vitaminproblem: I. Mitteil., Untersuchungen über das Gasstoffwechsel avitaminotisch ernährter weisser Mäuse, Ztschr. f. phys. Chem. **122**:104, 1922; Klin. Wchnschr. 1548, 1922; II. Mitteil., Untersuchungen über den Einfluss der Vitaminzufuhr und des Hungerns auf Gasstoffwechsel, Gewicht und Lebensdauer vitaminfrei ernährter weisser Mäuse, Ztschr. f. phys. Chem. **131**:214, 1923; III. Mitteil., Weitere Untersuchungen über den Einfluss der Vitaminzufuhr auf Gaswechsel, Gewicht und Lebensdauer vitaminfrei ernährter weisser Mäuse, ibid. **137**:14, 1924.

9. Knipping and Kowitz: Untersuchungen über die Avitaminose beim Menschen, München. med. Wchnschr. **70**:46 (Jan. 12) 1923.

Contrary to the observations of previous workers, Magne and Simonnet [10] found that in pigeons neither the respiratory quotient nor the consumption of oxygen changed as the result of vitamin starvation.

Bickel [11] and his co-workers made numerous experiments on animals to determine the metabolism in vitamin starvation. Bickel concluded from these investigations that the irritation period of avitaminosis, as he calls it, during which there may be an increase in body weight, is not long, and that two phenomena soon appear: a decrease in consumption of oxygen and the invasion of the blood by sugar and fat as a consequence of the evacuation of glycogen and fat, both being an expression of a powerful stuff mobilization. The decrease in consumption of oxygen and body weight is observed when sufficient calories of food are absorbed. Bickel finds the absorption of food even greater during prolonged vitamin starvation than during a normal period when there are no disturbances of the stomach and intestine. From these observed phenomena it is clear that the decreased consumption of oxygen is a primary symptom of avitaminosis, and that it has nothing to do with the disturbance of absorption in the intestinal tract, that is, with undernutrition or hunger. The oxidation of protein and fat has been proved to increase during vitamin starvation, and this with retardation of sugar catabolism causes a lowering of the respiratory quotient. The intake of oxygen and the elimination of carbon dioxide are diminished, and as the protein catabolism continues in an almost normal manner, so that increased consumption of oxygen is required because of the increased protein catabolism and also because of the intermediate metabolism, at least in the usual relation of avitaminosis, evidences of disturbance in the oxidation of fat are not perceivable; on the contrary, an increased and continuous fat catabolism occurs in the whole organism. Sugar catabolism must go on with decreased consumption of oxygen and consequent decrease in the elimination of carbon dioxide. Notwithstanding the increased protein and fat catabolism, the basal metabolism, measured by gas exchange, is distinctly diminished. This is the case in actual avitaminosis, in which food containing enough calories of protein, fat and carbohydrate is thoroughly absorbed. This is possible only when the oxidation of sugar, and, as a result, the production of carbon dioxide, are extraordinarily restricted, and necessitate an increase in the consumption of oxygen and protein and probably of fat, accompanied by an increase in the production of carbon dioxide through oxidation of sugar. As carbohydrate is also thoroughly absorbed, the dysoxidizable

10. Magne, H., and Simonnet, H.: Sur les variations du quotient respiratoire chez le pegeon carencé, Bull. Soc. de chem. biol. **4**:419, 1922.

11. Bickel, A.: Das Wesen der Avitaminose. Nach experimenteller Untersuchungen über die Abmagerungsform dieser Krankheit, Biochem. Ztschr. **146**: 493, 1924; Weitere Untersuchungen über den Stoffwechsel bei der Avitaminose, ibid. **166**:251, 1925.

products thus must accumulate in the body or may be eliminated in the urine. Urinalysis showed that by avitaminosis the dysoxidizable carbon of the urine increases, and, notwithstanding the excretion of nitrogen, is at first unchanged, and later increased; and that the urine quotient—carbon: nitrogen—becomes higher. In the middle period of the disease, perhaps accompanied by the elimination of fat, the quotient is especially high, showing some decrease at a later stage, but it is always pathologically high. The increase of lactic acid in the urine during avitaminosis is slight and cannot explain the marked increase in the quotient.

Yanagi [12] determined the consumption of oxygen of rats and human subjects in vitamin starvation; in general, he found a significant decrease, with more or less fluctuation. When the animals were fed with diets containing some but not a sufficient amount of vitamins, the body weight increased during the first two or three weeks, followed by a decrease later. The consumption of oxygen, however, was diminished when the body weight still continued to increase, and became more significant and especially marked when paralysis developed. During the last period, it sometimes tended to increase again. After the administration of vitamin B preparations, the consumption of oxygen increased promptly with appetite and body weight if the paralysis was not too extreme.

Goh [13] observed the gas exchange in pigeons during the course of relative insufficiency of vitamins. These pigeons showed symptoms of avitaminosis for from one hundred and thirty-one to two hundred and twenty-four days after the beginning of the special diet. The respiratory quotient gradually became lower during the period of incubation, about twenty days before polyneuritis appeared. During the period of polyneuritis it became especially low, in all cases being less than 0.7. The intake of oxygen, however, was unchanged or increased. The author concluded from this result that in avitaminosis the oxidation of carbohydrate is extremely disturbed.

Odaira [14] reported that the basal metabolism becomes lower in the course of vitamin poor alimentation, although there is not a significant decrease, and again becomes higher when cardiovascular symptoms become marked.

To summarize: The important observations on the gas metabolism in vitamin B starvation are that a decrease occurs in the consumption of oxygen as well as in the production of carbon dioxide, that is, a lowering of the basal metabolism; in some instances, there is a marked decrease in the elimination of carbon dioxide, that is, a diminution of the respiratory quotient. In reviewing the protocols, however, the observations do

12. Yanagi, K.: The Oxygen Consumption in Vitamin B. Starvation, Nippon Naika Gakukwai Zasshi **13**:189, 1925; Nippon Seikagakukai Kaiho **1**:50, 1926.
13. Goh, T.: Nippon Byori Gakukwai Kaishi, **15**:469, 1926.
14. Odaira, T.: Nissin Igaku, **15**:1659, 1926.

not coincide; some even contradict each other; this is due perhaps to the conditions of the experiments and to the methods applied, but the most important factor is the difference in the materials employed. Perhaps we were the first to attempt a systematic investigation of gas metabolism in human beings during vitamin B starvation, although it was reported previously in one case by Caspari and Moszkowski. A detailed description of our observations therefore does not seem superfluous.

We made two series of investigations, one to determine the influence of vitamin B starvation on the basal metabolism in beriberi, the other to determine, if possible, whether any deviation in the gas metabolism may occur during the course of vitamin B starvation in normal persons.

METHOD

The material studied consisted of four patients with typical symptoms of beriberi and five healthy men. The patients with beriberi were examined carefully, and no complications were found with the exception of some parasites' eggs in the feces. The healthy subjects volunteered for the experiment. The diet for the patients with beriberi during the experiment was especially restricted. The main food consisted of well polished and thoroughly washed rice; the supplementary food consisted of beef, koyadofu, konyaku, fukujinzuké, lard, cane sugar, wheat meal, miso, soya and salts. The beef was boiled for two hours with 1.2 per cent caustic soda; it was then neutralized to a faintly acid reaction with acetic acid, and boiled. Konyaku was autoclaved from two to three hours at from 130 to 170 C. Food was selected which contained enough protein, fat, carbohydrate and salts. The meals were then adjusted to obtain the proper number of calories. For example, in case 1, breakfast consisted of 300 Gm. of boiled rice, 30 Gm. of miso, 10 Gm. of fukujinzuké and one piece of koyadofu; lunch consisted of 300 Gm. of boiled rice, one piece of koyadofu, 5 Gm. of sugar, 20 cc. of soya and 10 Gm. of fukujinzuké and dinner consisted of 300 Gm. of boiled rice, 100 Gm. of beef, 10 Gm. of lard, 10 Gm. of wheat powder, 10 Gm. of fukujinzuké and 10 Gm. of salt, a total of 1,850 calories. The amount of protein in these meals was 79.3 Gm.; fat, 25.3 Gm., and carbohydrate, 315 Gm. Vitamin B, however, was almost completely lacking, which was proved also by feeding pigeons with a pulverized mixture of these foods; as a consequence, a typical paralysis and convulsion occurred. Vitamin A (biosterin) was administered in liquid form. Three of the healthy subjects were fed on a relatively restricted diet, and all showed typical symptoms of avitaminosis after a period of incubation. Two others were fed on a slightly restricted diet which was not much different from the usual diet in the wards. After an observation of eighty-five and one hundred and twenty-three days, respectively, no symptoms were seen. Therefore, in these last two cases, although the vitamin B content was not rich, it was not deficient.

The metabolic rates were obtained by the gasometer method with analysis of the expired air by the Haldane gas analysis apparatus. The technic of Boothby and Sandiford was followed.

REPORT OF CASES

Case 1.—B. S., a youth, aged 15 years and 2 months, entered the hospital with a condition diagnosed beriberi. His family history was unimportant. He had had measles when a child, appendicitis at the age of 9, and some febrile disease at the age of 13 had confined him in bed for about one hundred days.

In the beginning of January, 1922, he felt numbness of the legs. On the 29th of that month, he was suffering from a cold; he had a mild headache and

a cough; his temperature was 39 C. (102.2 F.), and he was confined to bed. The fever continued until the middle of February. The numbness and hypesthesia extended up to the abdomen. Paralysis of the lower limbs developed, and the patient was unable to walk; but as the arms were not affected, he continued in his occupation (book-binding). On May 3 he visited the dispensary, and two days later he was admitted to the hospital.

Examination revealed a well nourished and vigorous man of medium height, somewhat pale. The pupillary reflexes were normal. The teeth and tonsils were in good condition. The tongue was rather dry and furred. Neither fever nor edema was present. The pulse rate was 80; it was strong, regular and moderately resistant to presure. The thyroid gland was somewhat enlarged.

TABLE 1.—*Metabolism Data on Patient with Beriberi (Case 1*)*

Date, 1922	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
5/25	48.8	1.46	80	29	0.74	47.9	+ 4.1	36.5	Usual diet
5/ 1	47.8	1.45	90	21	0.81	48.0	+ 4.3	36.6	Usual diet
6/ 5	48.5	1.46	100	16	0.80	45.8	— 0.4	36.4	Usual diet
6/30	45.0	1.41	75	14	0.76	43.3	— 5.8	36.5	Usual diet
7/13	46.2	1.43	82	19	0.78	42.1	— 8.5	36.4	Vitamin free 1 day
7/16	46.2	1.43	92	19	0.76	39.1	—15.0	36.3	Vitamin free 4 days
7/19	45.3	1.42	77	20	0.76	36.2	—21.3	36.5	Vitamin free 7 days
7/21	45.6	1.42	92	17	0.79	36.6	—20.4	36.6	Vitamin free 9 days
7/22	46.0	1.43	90	21	0.74	41.1	—10.6	36.4	Vitamin free + oryzanin powder 3.3 Gm. + oryzanin solution 13.3 cc.
7/26	45.7	1.42	72	19	0.75	41.5	— 9.8	36.2	Vitamin free + oryzanin solution 40 cc. 1 day
8/ 1	45.7	1.42	86	20	0.96	46.1	+ 0.2	36.5	Vitamin free + oryzanin solution 40 cc. 7 days
8/ 7	44.8	1.41	90	20	0.93	46.1	+ 0.2	36.5	Vitamin free + oryzanin solution 40 cc. 13 days
8/ 9	44.8	1.41	78	22	0.94	37.6	—18.3	36.3	Vitamin free + autoclaved oryzanin 10 Gm. 2 days
8/11	45.4	1.42	72	19	0.92	35.3	—23.2	36.4	Vitamin free + autoclaved oryzanin 10 Gm. 4 days
8/13	45.4	1.42	68	20	0.81	38.1	—17.2	36.3	Vitamin free + autoclaved oryzanin 10 Gm. 6 days
8/15	45.3	1.42	80	17	0.97	37.0	—19.6	36.2	Vitamin free + autoclaved oryzanin 10 Gm. 8 days
8/17	45.4	1.42	88	17	0.97	36.6	—20.5	36.5	Vitamin free + autoclaved oryzanin 10 Gm. 10 days
8/21	45.0	1.41	80	18	0.80	43.2	— 6.1	36.3	Vitamin free + oryzanin powder 10 Gm. 3 days
8/25	45.9	1.42	70	20	0.92	43.1	— 6.3	36.4	Vitamin free + oryzanin powder 10 Gm. 7 days
8/29	47.5	1.44	68	20	0.94	41.8	— 9.1	36.0	Vitamin free + oryzanin powder 10 Gm. 11 days
9/13	46.3	1.43	72	21	0.94	42.7	— 7.2	36.4	Usual diet 5 days
9/ 7	45.9	1.42	92	18	0.85	41.7	— 9.3	36.2	Usual diet 9 days

* B. S., boy, aged 15 years and 2 months, 156.2 cm. in height.

There was a slight dulness over the right side of the collarbone. The heart was enlarged on both sides; the area of absolute dulness reached to the right sternal margin, to the upper margin of the fourth rib and the line of the left nipple. The systolic sound at the apex was somewhat impure, and the second pulmonic sound was slightly accentuated. The crural sound was rustling, and brachial sound was low and dull. The abdomen was somewhat distended. The liver was palpable two fingerbreadths under the costal arch and somewhat tender. There was no numbness; the arms were not affected; talipes equinus was present; motility of the lower limbs, especially the act of raising them, was impaired. Hypesthesia and hypalgia of the legs and the dorsa of the feet were noticeable; these areas were partly anesthetic. The sole was free from disturbances of sensibility. The knee and achilles reflexes were present. The cremasteric reflex was positive. The blood count showed 4,828,000 red blood cells, 80 per cent hemoglobin and 6,800 leukocytes, of which 45.2 per cent were polymorphonuclear neutrophils, 36 per

cent lymphocytes, 8.4 per cent eosinophils and 10.4 per cent mononuclears and transitory forms. The blood pressure was: right side, systolic 141 and diastolic 0; left side, systolic 142 and diastolic 0.

The main clinical observations after vitamin B starvation (ten days' duration) were: no marked change in weight, edema (±), no variation in the quantity of urine, loss of appetite since the fifth day and nausea on the sixth day. There was tenderness of the calf muscles before vitamin B starvation, which increased on the ninth to the eleventh day. The pulse rate had gradually increased since the third day; on the sixth day it was 126, on the tenth day 108 and on the fifth day distinctly dicrotic. The blood pressure just before the patient was placed on a restricted diet was: right side, systolic 129 and diastolic 50; left side, systolic 132 and diastolic 62. On the third day the diastolic pressure began gradually to decrease; on the right side it was systolic 131 and diastolic 0; on the left, systolic 134 and diastolic 0. If the intensity of the crural sound before vitamin B starvation is expressed as +, on the sixth day it was ++ and on the ninth +++. The brachial sound before the beginning of the restricted diet was —; on the sixth day and after vitamin B starvation, it was +. On the sixth day the patient became dyspneic; the heart was somewhat enlarged on both sides; there was accentuation of the second pulmonic sound, and the systolic murmur was louder. The chief changes were: loss of appetite, greatly increased tenderness of the calf muscles, increased pulse rate (124), decrease in diastolic blood pressure, sharp crural sound and dicrotism. All these symptoms were significantly ameliorated after a vitamin B preparation was administered.

The average basal metabolism at the time the patient was on his usual diet was + 0.2 per cent. During the nine days of the first experiment with vitamin B starvation, this average was — 16.3 per cent, and during the period of administration of oryzanin it was — 5 per cent. During the ten days of the second experiment with vitamin B starvation, the average metabolism was — 19.8 per cent, and during the last period with vitamin B starvation or the usual diet, it was — 7.6 per cent.

Case 2.—K. K., a man, aged 25, single, entered the hospital with a condition diagnosed beriberi. His paternal grandmother had died of apoplexy at the age of 72, his father had died of nephritis at 69, and his mother had died of an unknown disease at 63. The patient had four brothers and sisters, all of whom were healthy. A nephew had died of acute decompensation (cardiac form of beriberi). The patient had had measles when a child; otherwise he had always been healthy. In June, 1926, he returned from military service, and resumed his work as a peasant. His main food was polished rice. During the latter part of August the patient felt numbness of the legs, weakness of the calf muscles, especially when walking, and looseness of the knee joints, so that he tired readily. Edema appeared over the tibia and the dorsa of the feet. In the middle of September palpitation and dyspnea appeared on movement, and he was unable to walk. On September 16 the symptoms were aggravated, and decompensation appeared, accompanied by oppression, nausea, eructation and vomiting. He became unconscious, from which state he fortunately recovered. On November 6 he again had decompensation and was confined to his bed for about thirty days. He could walk a little during the latter part of December. In March of this year he again worked in the field, after which he felt weak and noticed edema. He was admitted to the hospital on June 3.

Examination revealed a well nourished and vigorous man of medium height. A slight cyanosis of the lips and fingertips was present. The pupillary reflexes were normal. The tongue was moist and slightly furred. He had a tremor. The pulse rate was 75; it was regular and moderately resistant to pressure. The blood pressure was: 126 systolic and 62 diastolic, and did not indicate that scelosis was present. Respiration was 22, regular and of the costo-abdominal type. Expiration at the right apex of the lung was somewhat prolonged and high pitched. The apex beat was diffuse and heaving. (The left border of the heart was one-half fingerbreadth inside of the nipple line.) The systolic sound at the apex was somewhat dull; the second pulmonic sound was slightly accentuated and if it

occurred coincident with expiration, it was split. The crural sound was audible. The gait was wide and waddling. There was hypesthesia from the costal arch and from the middle of the back downward. The epigastric and cremasteric reflexes were positive. Knee and achilles reflexes were present. The tenderness of the calf muscles was significant. Edema was not present. Urinalysis showed a specific gravity of 1,027, and a urine the color of beer and slightly alkaline. The sulphosalicylic test was opalescent; the indican test was negative. The blood count showed 5,740,000 red blood cells, 95 per cent hemoglobin and 7,500 leukocytes, of which 67.5 per cent were polymorphonuclear neutrophils, 21 per cent lymphocytes, 8 per cent eosinophils, 0.5 per cent basophils and 3 per cent mononuclears and transitory cells.

The main clinical observations after vitamin B starvation (seven days' duration) were: A slight decrease in weight, edema, a sudden decrease in the quantity of urine from 1,600 cc. to 200 cc. The patient lost his appetite on the fifth day, and nausea and vomiting occurred three times on the sixth day. Flaccidity and tenderness of the calf muscles appeared. The pulse rate had gradually increased

TABLE 2.—*Metabolism Data on Patient with Beriberi (Case 2*)*

Date, 1922	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
6/29	58.5	1.59	90	16	0.71	41.2	+ 4.3	36.7	Usual diet
6/30	58.4	1.58	84	18	0.75	40.9	+ 3.5	36.2	Usual diet
7/4	59.1	1.59	80	19	0.74	41.6	+ 5.5	36.2	Usual diet
7/10	58.7	1.59	75	21	0.79	41.6	+ 5.5	36.2	Usual diet
7/13	57.8	1.57	60	21	0.72	39.1	— 1.0	35.8	Vitamin free 1 day
7/16	57.8	1.57	76	20	0.74	37.8	— 4.3	36.2	Vitamin free 4 days
7/18	57.0	1.56	86	24	0.68	35.8	— 9.4	37.2	Vitamin free 6 days
7/21	58.8	1.58	75	21	0.90	37.5	— 5.1	37.0	Vitamin free + spelzon 40 cc.
7/23	57.8	1.57	64	20	0.81	41.8	+ 5.8	36.5	Vitamin free + spelzon 40 cc.
8/1	55.5	1.55	62	20	0.77	42.3	+ 7.1	36.1	Vitamin free + spelzon 40 cc.
8/3	55.9	1.55	58	21	0.73	38.6	— 2.3	36.1	Vitamin free 2 days
8/5	55.5	1.55	64	20	0.74	37.5	— 5.1	36.0	Vitamin free 4 days
8/7	56.0	1.55	66	20	0.77	33.7	—14.7	36.3	Vitamin free 6 days
8/9	56.2	1.55	70	22	0.93	31.4	—20.5	36.5	Vitamin free 8 days
8/11	56.8	1.56	78	20	0.90	32.4	—17.9	36.4	Vitamin free 10 days
8/13	57.7	1.57	68	21	0.78	35.0	—11.4	36.3	Diet with vitamin
8/14	57.9	1.57	66	20	0.78	38.8	— 1.7	36.2	Diet with vitamin
8/19	58.3	1.58	70	22	0.93	39.7	+ 0.5	35.8	Usual diet
8/23	58.1	1.58	84	23	0.81	40.0	+ 1.3	36.3	Usual diet

* K. K., man, aged 25, 156.3 cm. in height.

since the fourth day; on the sixth day it was 110. The blood pressure before the patient was placed on a restricted diet was 116 systolic and 30 diastolic on the right side, and 109 systolic and 68 disastolic on the left; on the fifth day it was 99 systolic and 0 diastolic on the right, and 99 systolic and 40 diastolic on the left. The crural sound became sharp; the brachial sound before the restricted diet was not heard; on the fifth day it was audible. Palpitation before vitamin B starvation did not occur; on the fourth day there was palpitation even when the patient was in bed. The heart was somewhat enlarged. The chief changes were: diminution in the quantity of urine, loss of appetite, vomiting, increased pulse rate and sharp crural sound.

The average basal metabolism diminished during vitamin B starvation. When the patient was on his usual diet, the average basal metabolism was + 4.5 per cent; during the seven days of the first experiment with vitamin B starvation, this average was — 4.8 per cent, and during the period of vitamin B medication it was — 2.5 per cent. During the second experiment, when the patient did not receive any vitamins, the average metabolism was — 12.1 per cent, and when he received a vitamin B preparation or the usual diet it was — 2.8 per cent.

CASE 3.—S. A., a man, aged 22, was admitted to the hospital with a condition diagnosed beriberi. His family history was unimportant. He had had measles when a child and had been vaccinated many times. During the latter part of

April, 1926, the patient suffered from distention and a full sensation at the epigastrium, sometimes nausea, vomiting and pain in the region of the stomach. The appetite was deficient. About the middle of May he returned to his home, and the symptoms became milder. He was admitted to the hospital on July 30, after his symptoms had been more severe for five or six days.

Examination revealed a well nourished and vigorous man, somewhat small; the subcutaneous fat tissue was well developed, and the expression was natural. He had cyanosis and tremor at the fingertips. The tongue was moist and coated. Dermography was present. The pulse was normally resistant to pressure, strong

TABLE 3.—*Metabolism Data on Patient with Beriberi (Case 3 *)*

Date, 1922	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
8/ 3	48.8	1.44	60	16	0.89	39.8	+ 0.8	36.5	Usual diet
8/ 5	48.1	1.44	64	15	0.90	40.3	+ 2.3	36.2	Usual deit
8/16	48.5	1.44	58	15	0.83	40.2	+ 1.8	36.2	Vitamin free + oryzanin 4.5 Gm. 1 day
8/18	47.3	1.42	70	16	0.76	37.7	— 4.5	36.9	Vitamin free + oryzanin 4.5 Gm. 3 days
8/22	47.1	1.42	56	15	0.79	37.7	— 4.5	35.9	Vitamin free + oryzanin 6 Gm. 3 days
8/21	47.3	1.42	56	15	0.90	34.1	—13.6	36.0	Vitamin free + autoclaved oryzanin 6 Gm. 2 days
8/26	47.7	1.43	60	19	0.93	32.8	—16.9	36.0	Vitamin free + autoclaved oryzanin 6 Gm. 4 days
8/28	47.0	1.42	60	20	0.85	36.0	— 8.8	....	Vitamin free + autoclaved oryzanin 6 Gm. 6 days
8/30	47.1	1.42	58	15	0.82	33.1	—16.2	35.7	Vitamin free + autoclaved oryzanin 6 Gm. 8 days
9/ 1	46.8	1.42	60	13	0.78	30.8	—22.0	36.4	Vitamin free + autoclaved oryzanin 6 Gm. 10 days
9/ 3	46.4	1.42	60	14	0.78	32.9	—16.7	36.3	Vitamin free + autoclaved oryzanin 6 Gm. 12 days
9/ 5	46.7	1.42	66	14	0.84	31.8	—19.5	36.1	Vitamin free + autoclaved oryzanin 6 Gm. 14 days
9/ 7	46.5	1.42	60	13	0.82	31.7	—19.7	36.1	Vitamin free + autoclaved oryzanin 6 Gm. 16 days
9/ 9	46.2	1.41	60	22	0.79	32.4	—17.9	35.9	Vitamin free + autoclaved oryzanin 6 Gm. 18 days
9/11	46.0	1.41	65	13	0.82	32.9	—16.7	36.1	Vitamin free + autoclaved oryzanin 6 Gm. 20 days
9/13	46.0	1.41	62	18	0.78	26.1	—33.9	36.3	Vitamin free + autoclaved oryzanin 6 Gm. 22 days
9/15	45.0	1.39	60	13	0.74	36.1	— 8.6	35.5	Vitamin free + oryzanin 6 Gm. 2 days
9/17	45.5	1.40	60	11	0.73	36.3	— 8.1	35.4	Vitamin free + oryzanin 6 Gm. 4 days
9/19	45.7	1.40	56	20	0.76	37.1	— 6.1	36.1	Vitamin free + oryzanin 6 Gm. 6 days
9/21	45.7	1.40	66	14	0.76	37.1	— 6.1	36.0	Vitamin free + oryzanin 6 Gm. 8 days
9/24	45.8	1.40	60	13	0.72	38.8	— 1.7	36.1	Vitamin free + milk 300 cc. 2 days
9/28	46.0	1.41	64	12	0.83	37.1	— 6.1	36.3	Vitamin free + milk 300 cc. 6 days

* S. A., man, aged 22, 153.7 cm. in height.

and regular; the blood vessels were neither sclerotic nor tortuous. The respiration was of the costo-abdominal type. The apex beat was scarcely noticeable, one fingerbreadth inside of the nipple line in the fifth intercostal space. The area of absolute dulness extended from the left sternal margin to the upper edge of the fourth rib and the line of the left nipple; the area of relative dulness extended from the right sternal margin to the upper edge of the third rib and half a fingerbreadth outside of the nipple line. At the apex the first sound was impure; the second pulmonic sound was accentuated and split (by inspiration). The crural and brachial sounds were not distinctly audible. The knee reflexes were weak, and the achilles reflex was present. Motility was not affected. During the latter part of April hypesthesia appeared, and in June it extended from the toes to the middle of the abdomen. The sole of the foot was not affected.

The main clinical observations after vitamin B starvation (twenty-two days' duration) were: a slight decrease in weight (about 1 Kg.), absence of edema and slight variation in the quantity of urine. The patient was constipated (once for four days); he lost his appetite on the fifth day; general flaccidity and dulness had been present since the sixth day and numbness since the fourth day. There was no marked change in the pulse rate; the blood pressure was without significance. The crural sound had been noticeable since the seventh day and the brachial sound since the tenth day. The chief changes were: constipation, increased tenderness of the calf muscles and exaggeration of the vessel sounds.

The average basal metabolism during the time the patient was on his usual diet was —1 per cent, during vitamin B starvation —18.5 per cent and during the time of vitamin B medication or when the patient drank milk —6.1 per cent.

Case 4.—M. O., a man, aged 22, was admitted to the hospital on Aug. 17, 1926, with a condition diagnosed beriberi. The family history was unimportant. The patient had had measles when a child and had been vaccinated may times. At the age of approximately 10 years, he suffered from pleurisy after falling from a tree. At the age of 19, he suffered from influenza and was in bed for about three days. Both tonsils had been removed in 1926. Defecation occurred once every day. Early in June he had felt numbness and heaviness of the dorsa of the feet, and in the beginning of August there was numbness of the fingertips. The looseness of the knee caused him to fall. He did not experience thirst, but he perspired occasionally, and there was no edema.

The patient was moderately nourished; his expression was natural. He was not anemic. The tongue was clean, moist and without tremor. The face and the body were dry, but the dorsa of the feet were moist. The pupillary reflex was positive. Respiration was of the costo-abdominal type. There was no sclerosis of the vessels. The apex beat was in the fifth intercostal space on the nipple line. The area of relative dulness extended from one and one-half fingerbreadths outside of the right sternal margin to the upper edge of the third rib and half a fingerbreadth beyond the line of the left nipple. The second pulmonic sound was accentuated, and the first sound at the apex was impure. The crural sound was sharp but not loud, with a murmur; the brachial sound was audible with a murmur. The right arm was somewhat weaker than the left. The mucous membrane was not affected. Knee jerks were present; the achilles reflex on the right side was doubtful; on the left, absent. The calf muscles, especially on the inner side, were somewhat hard; there was no edema or glandular swelling; the right kidney was palpable. Urinalysis showed: specific gravity, 1.031; a reddish-yellow and acid urine; no protein or sugar; indican ++. In the blood, there were 4,590,000 red blood cells, 90 per cent hemoglobin and 5,200 leukocytes, of which 53.2 per cent were polymorphonuclear neutrophils, 36.5 per cent lymphocytes, 6.2 per cent eosinophils, 0.2 per cent basophils and 4.7 per cent transitory cells.

The main clinical observations after vitamin B starvation (thirteen days' duration) were: a slight increase in weight during the beginning, no edema, no variation in the quantity of urine, defecation once a day until the third day, when constipation and loss of appetite occurred. Tenderness of the calf muscles since the third day was +, and since the tenth day ++. The chief changes were: constipation, loss of appetite and tenderness of the calf muscles.

The average metabolism during the times the diet was free from vitamin B and the patient was receiving vitamin B preparation was +2.5 per cent; during vitamin B starvation it was —13.7 per cent and with vitamin B preparation or with milk it was —5.8 per cent.

From the foregoing descriptions it can be seen that the four patients with beriberi always showed more or less aggravation of symptoms after vitamin B starvation, especially when the cardiovascular system was mainly involved (cases 1 and 2). The danger of decompensation made

further continuance of the avitaminous alimentation dangerous. In all cases the basal metabolism showed distinct decrease during vitamin B starvation (without vitamin or with autoclaved, that is, destroyed vitamin) and increase after the addition of vitamin. The respiratory quotient showed no remarkable change during the course of the vitamin B starvation. There was loss of appetite in all cases, and the intake of food was diminished, but the decrease in basal metabolism

TABLE 4.—*Metabolism Data on Patient with Beriberi (Case 4*)*

Date, 1922	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
8/21	47.1	1.47	56	21	0.78	40.2	+ 1.7	36.1	Vitamin free diet + oryzanin 6 Gm.
8/23	47.1	1.47	55	23	0.80	40.7	+ 3.0	36.2	Vitamin free diet + oryzanin 6 Gm.
8/25	47.6	1.47	60	22	0.78	36.1	— 8.6	35.8	Vitamin free diet + autoclaved oryzanin 6 Gm. 2 days
8/27	47.5	1.47	58	22	0.84	34.2	—13.4	35.9	Vitamin free diet + autoclaved oryzanin 6 Gm. 4 days
8/29	47.0	1.47	60	21	0.90	32.6	—17.4	36.7	Vitamin free diet + autoclaved oryzainin 6 Gm. 6 days
8/31	46.3	1.46	66	17	0.75	34.7	—12.2	36.0	Vitamin free diet + autoclaved oryzanin 6 Gm. 8 days
9/ 2	46.2	1.46	63	18	0.87	32.7	—17.2	36.9	Vtamin free diet + autoclaved oryzanin 6 Gm. 10 days
9/ 4	47.2	1.47	79	18	0.87	34.2	—13.4	36.9	Vitamin free diet + autoclaved oryzanin 6 Gm. 12 days
9/ 6	47.2	1.47	61	20	0.85	35.8	— 9.3	36.0	Vitamin free diet + oryzanin 6 Gm.
9/ 8	46.3	1.46	58	10	0.82	37.3	— 5.6	36.0	Vitamin free diet + oryzanin 6 Gm.
9/10	45.8	1.45	46	14	0.78	35.0	—11.4	35.4	Vitamin free diet + oryzanin 10 Gm.
9/12	44.8	1.44	44	16	0.87	36.6	— 7.3	35.7	Vitamin free diet + oryzanin 10 Gm.
9/14	43.2	1.42	40	18	0.77	38.4	— 2.9	35.7	Vitamin free diet + oryzanin 10 Gm.
9/16	42.6	1.41	42	13	0.73	37.5	— 5.1	35.7	Vitamin free diet + oryzanin 10 Gm.
9/18	42.6	1.41	72	17	0.76	34.8	—11.9	35.3	Vitamin free diet + oryzanin 10 Gm.
9/20	42.8	1.41	45	17	0.90	34.4	—12.9	35.7	Vitamin free diet + oryzanin 10 Gm.
9/22	42.8	1.41	45	19	0.78	37.9	— 4.0	35.7	Vitamin free diet + oryzanin 10 Gm.
9/24	43.0	1.41	44	19	0.90	40.4	+ 2.3	36.0	Vitamin free diet + oryzanin 10 Gm.
9/26	43.3	1.42	50	15	0.85	40.3	+ 2.0	36.2	Vitamin free diet + milk 600 cc.
9/28	43.2	1.42	48	12	0.96	40.7	+ 3.0	36.3	Vitamin free diet + milk 600 cc.

* M. O., man, aged 21, 161 cm. in height.

was proved to occur at the time when the intake of food was still sufficient, or when a great deal of nourishment was taken on the previous day. The body weight was slightly diminished in one case (1 Kg.), while in others there was some increase, partly the result of edema. Therefore decrease in basal metabolism is not to be attributed to simple starvation; it seems to have an intimate relation to deficiency in vitamin B. The foregoing experiments are not sufficient to decide this question; healthy persons should be subjected to long continued vitamin B starvation until typical symptoms of avitaminosis develop, and the variation in basal metabolism should be noted. As we found that a

diet which induces avitaminosis soon causes a loss of appetite, it seems reasonable to arrange a diet which is slightly restricted, but which does not contain sufficient vitamin B. The research in cases 5 to 9 was carried out for this purpose.

CASE 5.—S. A., a man, aged 25, single, a healthy peasant, whose family history was unimportant, had had measles when a child, and had been vaccinated many times. His history was not suggestive of beriberi. He took saké (Japanese wine), about two glasses (400 cc.) occasionally, and used tobacco (twenty cigarets a day).

The patient was well nourished and vigorous and of medium height. The pupillary reflexes were normal. The tongue was moist and clean, and the left tonsil was somewhat enlarged. The pulse rate was 72; it was regular and moderately resistant to pressure. Respiration was 19 and was costo-abdominal in type.

TABLE 5.—*Metabolism Data on Healthy Patient (Case 5*)*

Date, 1923	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
11/ 2	50.6	1.48	53	14	0.79	38.9	— 1.5	36.3	Usual diet
12/ 3	51.0	1.49	56	16	0.77	41.0	+ 3.7	36.3	Usual diet
12/12	49.9	1.48	51	23	0.74	41.3	+ 4.5	36.3	Usual diet
12/13	50.0	1.48	52	23	0.75	43.1	+ 8.9	36.5	Usual diet
12/22	49.6	1.47	56	19	0.95	35.5	—10.1	36.2	Vitamin poor diet 9 days
12/26	49.8	1.48	56	16	0.91	37.6	— 5.0	36.3	Vitamin poor diet 13 days
12/27	49.6	1.47	53	18	0.90	35.7	— 9.7	36.2	Vitamin poor diet 14 days
1924									
1/12	50.0	1.48	60	16	0.79	36.6	— 7.3	36.4	Vitamin poor diet 30 days
1/16	50.8	1.48	56	28	0.74	38.3	— 3.1	36.3	Vitamin poor diet 34 days
1/17	51.3	1.49	59	18	0.83	35.0	—11.4	36.4	Vitamin poor diet 35 days
2/ 2	51.1	1.49	55	22	0.81	24.3	—37.0	36.1	Vitamin poor diet 51 days
2/16	51.8	1.50	58	25	0.70	31.6	—20.0	36.8	Vitamin poor diet 65 days
2/23	52.4	1.51	71	21	0.83	38.6	— 2.3	37.2	Vitamin poor diet 72 days
3/ 1	52.8	1.51	62	23	0.79	36.8	— 6.7	36.4	Vitamin poor diet 78 days
3/ 8	53.5	1.52	66	24	0.66	38.3	— 3.0	36.3	Vitamin poor diet, 85 days
3/15	55.0	1.54	72	24	0.71	38.4	— 2.8	36.3	Vitamin poor diet 92 days
3/20	53.9	1.53	80	23	0.72	38.5	— 2.6	36.1	Vitamin poor diet 97 days
3/23	53.3	1.52	53	20	0.78	42.9	+ 9.0	36.0	Vitamin poor diet with vitamin B 3 days
3/28	52.1	1.50	60	19	0.75	46.2	+14.5	36.2	Vitamin poor diet with vitamin B 8 days
4/ 5	53.1	1.52	60	20	0.87	42.9	+ 8.7	36.5	Usual diet 5 days

* S. A., man, aged 26, 156.5 cm. in height.

The right apex was somewhat dull; expiration was prolonged. The area of absolute dulness extended from the midline to the lower edge of the fourth rib and one fingerbreadth inside of the line of the left nipple; the area of relative dulness extended from the right sternal margin to the lower edge of the third rib and just inside of the nipple line. The liver was palpable, but no abnormalities were found. Sigmoidea was also palpable. The abdominal and cremasteric reflexes were normal. The knee and achilles reflexes were slightly exaggerated. Urinalysis showed: specific gravity 1.019. The urine was slightly acid; it did not contain protein, sugar or indican, but a moderate number of granulated casts, leukocytes, tailed and pavement epithelia were found. Eggs of parasites (*Ankylostoma, Trichostrongylus orientalis* and *Trichocephalus dispar*) were present in the feces.

Beginning Dec. 13, 1923, a vitamin poor diet was administered. For example, the breakfast consisted of: 500 Gm. of boiled rice, 30 Gm. of miso, 400 cc. of tea without sugar; lunch consisted of 500 Gm. of boiled rice, 35 Gm. of tofukara, 15 Gm. of onion, 4 Gm. of aburagé, 7 cc. of soya and 200 cc. of tea; dinner consisted of 500 Gm. of boiled rice, 50 Gm. of green vegetable, 1.5 Gm. of fish, 15 cc. of soya, 3 Gm. of sugar and 500 cc. of tea. The rice was continued

every day in the same way; the accessory diet was changed somewhat, but within the limitations every day.

About the end of January, 1924 (about forty days after the patient was first placed on the vitamin poor diet), slight symptoms began to appear, such as tenderness of the calves, slight cramp in the right knee and slight heartburn. In the beginning of February the symptoms became especially significant. The heart was enlarged to the left (on the left border the area of absolute dulness was half a fingerbreadth inside of the nipple line; the area of relative dulness was at the nipple line). A systolic murmur was marked at the apex and tricuspidal ostium; the second pulmonic sound was slightly accentuated and split. When the patient was in the recumbent posture, the second pulmonic sound was distinctly accentuated; the systolic murmur was audible in all valve areas, being especially marked at the apex and in the tricuspid area. There was slight edema of the face and over the tibia, which from time to time became moderately significant. Transient tenderness of the ribs (from the seventh to the tenth) was also observed. On March 1, hypesthesia appeared on the inner side of the legs. The heart was enlarged on both sides and to the upper border. The crural sound was sharp. Weakness of the leg was noticed, but there was no disturbance of motility or coarse motion. Symptoms of the stomach and the intestine were not significant. The pulse rate was 72; it was regular, not soft and not fast. In the middle of March symptoms, such as a full sensation and heartburn appeared. Beginning on March 20, vitamin B preparation was administered. When the patient was sitting, the area of absolute dulness extended from the right sternal margin to the lower edge of the third rib and one-half fingerbreadth outside of the nipple line. The first tricuspidal and apex sound was impure and loud; the second aortic sound was accentuated. With vitamin B administration, there began to be relief from the symptoms. On April 10, the apex beat was one fingerbreadth inside of the line of the left nipple; the right border and the upper border were just as before, and the left border was just inside (absolute) and just outside (relative) of the nipple line. The heart sounds were all pure; the first aortic and the pulmonic sound were split. The liver was palpable one fingerbreadth under the right costal arch. The knee and achilles reflexes were exaggerated as before. Chaddock's sign was negative; there was no tenderness of the calves or edema. There were no disturbances of sensibility and no abnormalities in the urine.

The average basal metabolism when the patient was on his regular diet was +4 per cent; in vitamin B starvation it was −8.1 per cent, and with vitamin B medication, or when the regular diet was resumed, it was +11.4 per cent. During the period of vitamin B starvation, there was a distinct lowering of the basal metabolism.

Case 6.—T. N., a man, aged 28, was a healthy person whose family history was unimportant. The patient had had measles when a child, and had been vaccinated many times. At the age of 17, he had had syphilis and gonorrhea, but was not treated. The next year, he suffered from diphtheria, and thereafter was inclined to pharyngeal inflammation. He had also suffered from pneumonia about ten years before, from a disorder of the stomach about six years before and from typhoid fever in June, 1926. He took Japanese wine occasionally (200 cc). and used tobacco moderately. He had suffered from hernia inguinalis sinistra since childhood. He did not cough and did not raise sputum. He had worked at home as a peasant since childhood. He had not been in military service.

The patient was a well nourished and vigorous man somewhat short. His expression was natural. Moderate cyanosis and anemia were present. The tongue was moist and clean; the arch of the palate was congested. The muscles were well developed. The pulse rate was 82; it was rather low, soft and regular. Respiration was of the costo-abdominal type. The pupillary reflexes were normal. The right apex was somewhat dull; expiration was sharp and prolonged; there was sparse crepitation at both apexes. The area of absolute dulness was from the midline to the lower edge of the fourth rib and one and one-half fingerbreadths inside the nipple line; the area of relative dulness extended from the

right sternal margin to the lower edge of the third rib and one-half fingerbreadth inside of the nipple line. The first sound at the apex was hollow. When the patient was in a recumbent posture, a slight systolic murmur was audible at all valve areas. The second pulmonic sound was accentuated and split. The blood pressure was 108 systolic and 40 diastolic. Sensibility and motility were not affected. There was nothing unusual about the abdomen. The knee jerks were exaggerated, and the achilles reflex was normal. There were no abnormalities in the urine. Eggs of *Ankylostoma* and *Ascaris* were detected in the feces. The blood count showed 5,700,000 red blood cells, 65 per cent hemoglobin and 5,700 leukocytes, of which 62 per cent were polymorphonuclear neutrophils, 38.6 per cent lymphocytes, 4.8 per cent eosinophils, 0.4 per cent basophils and 2.4 per cent mononuclears.

Beginning Nov. 23, 1923, vitamin poor diet was administered as in case 5.

In the middle of December the patient complained of heartburn, eructation and a feeling of palpitation in the region of the stomach. He felt disgusted and

TABLE 6.—*Metabolism Data on Healthy Patient (Case 6*)*

Date, 1923	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
11/13	48.6	1.43	60	17	0.95	40.7	+ 3.0	36.1	Usual diet
11/17	48.8	1.44	61	17	0.79	41.8	+ 5.5	36.9	Usual diet
11/21	48.4	1.43	55	19	0.80	38.8	— 1.8	36.5	Usual diet
11/30	48.7	1.44	57	21	0.92	40.0	+ 1.8	36.8	Vitamin poor diet 7 days
12/1	48.9	1.44	57	18	0.92	36.8	— 6.7	36.7	Vitamin poor diet 8 days
12/14	48.3	1.43	65	18	0.69	36.0	— 8.9	36.4	Vitamin poor diet 21 days
12/15	48.5	1.43	56	18	0.75	35.5	—10.1	36.7	Vitamin poor diet 22 days
12/21	48.6	1.43	54	17	0.81	34.5	—13.0	36.5	Vitamin poor diet 28 days
12/22	48.6	1.43	62	14	0.82	36.5	— 7.6	36.5	Vitamin poor diet 29 days
12/25	48.1	1.43	67	15	0.88	36.7	— 7.0	36.9	Vitamin poor diet 63 days
1/24									
2/ 7	46.6	1.41	68	16	0.88	32.2	—18.6	36.3	Vitamin poor diet + vitamin B 7 days
2/13	47.1	1.42	63	15	0.89	31.4	—20.7	36.7	Vitamin poor diet + vitamin B 13 days
2/21	47.6	1.42	66	19	0.90	36.7	— 7.2	36.1	Vitamin poor diet + vitamin B 21 days
2/ 1	47.4	1.42	66	15	0.75	38.3	— 0.6	36.6	Vitamin poor diet + vitamin B 29 days
3/ 8	47.3	1.42	62	14	0.75	37.8	— 4.0	36.5	Vitamin poor diet + vitamin B 36 days
3/15	48.3	1.43	70	18	0.78	40.6	+ 2.8	36.6	Vitamin poor diet + vitamin B 43 days
4/ 5	47.8	1.42	64	19	0.81	38.0	— 3.7	36.7	Usual diet 15 days

* T. N., man, aged 28, 153 cm. in height.

nauseated when he saw food. In the middle of January, 1924, when he touched himself while bathing, the patient had a sensation as if paper had been drawn across the inside of the lower part of the legs and under the umbilicus. He complained of a looseness of the knee and slight bladder tenesmus. The symptoms of avitaminosis had become evident. The calves ached when he walked or when he moved his hip joints, and the stretching and bending power of the knee was weakened. During the latter part of January, the symptoms developed significantly. The patient complained of continued nausea, tenderness of the quadriceps and gastrocnemius, neuralgic pain and tenderness of the intercostal spaces and of the outer part of the upper part of the legs. He had developed a wide gait, and the raising of the toes was difficult. Slight edema appeared over the tibia. The patient complained of palpitation; the pulse rate was strong and fast, about 120 while the patient was sitting. Carotid pulsation when the patient was in a recumbent posture was significant. The liver was palpable one fingerbreadth under the right costal arch. The area of absolute dulness 0.5 cm. extended from the right of the right sternal margin to the lower edge of the third rib and the line of the left nipple; the area of relative dulness extended from

one fingerbreadth to the right of the right sternal margin to the upper edge of the third rib and 0.5 cm. outside the nipple line. The first sound at the apex was impure and weak; a systolic murmur was noted at the pulmonic ostium, and the second pulmonic sound was accentuated and split. The crural sound was sharp and accompanied by a systolic murmur. Plantar flexion of the right foot was somewhat weakened; dorsal flexion on both sides was weakened. The knee jerks on both sides were exaggerated. Beginning January 30, vitamin B preparation was administered. The symptoms became less marked, and on March 11, the heart border showed absolute dulness from the right sternal margin to the upper edge of the third rib and one fingerbreadth outside the nipple line. At the apex, the first and second sounds were hollow; the second pulmonic sound was split, but was no longer accentuated. At the beginning of April all symptoms were markedly ameliorated, and on the 21st of that month the patient left the hospital.

The basal metabolism at the time the patient was on his regular diet was + 2.3 per cent; during vitamin B starvation it was —7.3 per cent; with vitamin B

TABLE 7.—*Metabolism Data on Healthy Patient (Case 7 *)*

Date, 1923	Weight in Kg.	Body-Surface (DuBois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (DuBois)	Temperature, C.	Diet and Medication of the Previous Day
12/ 2	54.5	1.57	74	16	0.82	41.6	+ 5.3	35.8	Usual diet
12/ 3	54.3	1.56	71	14	0.89	37.1	— 6.1	36.4	Usual diet
12/12	53.4	1.54	69	17	0.67	41.6	+ 5.3	36.4	Usual diet
12/22	53.1	1.54	84	16	0.86	40.9	+ 3.6	36.1	Vitamin poor diet 9 days
12/27	53.5	1.55	79	14	0.94	39.2	— 0.8	36.2	Vitamin poor diet 14 days
12/29	53.5	1.55	67	20	0.63	38.5	— 2.5	36.3	Vitamin poor diet 16 days
1924									
1/12	54.1	1.55	70	14	0.77	40.3	+ 2.0	36.7	Vitamin poor diet 30 days
1/16	54.8	1.57	85	16	0.86	40.6	+ 2.8	36.3	Vitamin poor diet 34 days
1/27	54.5	1.57	83	15	0.75	40.3	+ 2.0	36.3	Vitamin poor diet 45 days
2/ 2	55.2	1.58	81	16	0.83	33.9	—14.2	36.3	Vitamin poor diet 51 days
2/ 9	55.9	1.59	85	17	0.75	40.9	+ 3.5	36.1	Vitamin poor diet 58 days
2/16	56.5	1.59	81	17	0.68	35.3	—10.7	36.6	Vitamin poor diet 65 days
2/23	54.9	1.57	74	16	0.65	38.7	— 2.0	36.4	Vitamin poor diet 72 days
2/28	52.3	1.53	73	14	0.61	37.5	— 5.0	37.7	Vitamin poor diet 77 days
3/ 4	52.6	1.53	78	16	0.68	31.6	—20.0	36.3	Vitamin poor diet 82 days
3/ 8	49.6	1.50	75	16	0.76	35.3	—10.7	36.9	Vitamin poor diet + vitamin B 4 days
3/14	54.5	1.57	70	17	0.88	36.5	— 7.5	36.4	Vitamin poor diet + vitamin B 10 days
3/18	49.8	1.50	70	17	0.71	44.5	+17.8	36.3	Vitamin poor diet + vitamin B 14 days
4/11	46.3	1.45	62	21	0.72	50.4	+27.5	36.7	Usual diet 18 days

* T. I., man, aged 24, 160 cm. in height.

medication or when the usual diet was resumed, it was —7.3 per cent. The last low value was due to the fact that it was low at the beginning of this period, gradually becoming higher later.

CASE 7.—T. I., a man, aged 23, single, a healthy person, was admitted to the hospital on Nov. 29, 1923. His family history was unimportant. He had had measles at the age of 7 and had been vaccinated many times. When he was 21 years of age, he worked as ironsmith in a factory from January to the following April. It was hard work, and he was obliged to stand usually for about ten hours every day. In July and August he noticed a slight edema over the tibia in the evening, which had disappeared the next morning after rest in bed. During the autumn this condition was not noticeable. Since April, 1926, he had been engaged again in agriculture, working about eight hours a day. In October an operation for hemorrhoids was performed; otherwise he had always been healthy. He took no alcohol, but used tobacco moderately.

The patient was a well nourished and vigorous man. The pupillary reflexes were normal; the tongue was moist, not furred and without tremor. The left tonsil was slightly enlarged and injected. The skin was normal. The muscles

were well developed. The pulse rate was somewhat low and weak, but regular. Respiration was of the costo-abdominal type. The right apex was slightly dull, and expiration was prolonged. At the lower part of the back on the right side the respiration murmur was somewhat weaker than on the left side. The area of absolute dulness extended from the midline to the lower edge of the fourth rib and two fingerbreadths inside the left nipple line; the area of relative dulness extended from the right sternal margin to the lower edge of the third rib and one-half fingerbreadth inside the nipple line. The first sound at the apex was somewhat impure; otherwise nothing of importance was noted. Motility and sensibility were not affected. The urine was normal. Eggs of *Ankylostoma* and *Trichocephalus* were detected in the feces. Beginning Dec. 13, 1923, the patient was placed on a vitamine poor diet (nearly the same as that in cases 5 and 6).

On Jan. 20, 1924 (about a month after the beginning of the vitamin poor diet), the lower part of the abdomen and both calves became slightly hypesthetic. The condition had grown significant at the end of that month. A trace of edema over the tibia, tenderness of the calves, weakness of the knee and achilles reflexes appeared. The crural sound was hollow, but distinctly reduplicated; the second pulmonic sound was accentuated when the patient was in a sitting position. At the beginning of February, the heart border was enlarged to the right side; the area of absolute dulness was the right sternal margin. There was a slight enlargement to the left (one and one-half fingerbreadths inside the nipple line). A systolic murmur was noticed at all valve areas when the patient was in a sitting position. When the patient was in a recumbent position, the second pulmonic sound was accentuated and impure. The pulse rate was 90; and it was strong, rapid dicrotic and soft. The patient stumbled often while walking. The joint of the knee slipped. The right knee reflex was absent and the left was extremely weak; the achilles reflex was absent. There was slight edema, which was quite evident, over the tibia; the face also was somewhat edematous. The hypesthetic zone was somewhat larger than before. The patient complained of a sensation of fulness, loss of appetite, distaste for food and eructation accompanied by nausea and vomiting. At the end of February symptoms of indigestion had become marked, and the intake of food was reduced. His legs were somewhat weak, and his gait was unsteady, so that the ascending of stairs was difficult. On February 29, he was unable to walk without support. Hypesthesia had become pronounced in front from the middle of the chest and in back from the middle of the gluteal region downward, including the soles of the feet; these areas were partly anesthetic. Edema of the face and over the tibia was pronounced. On March 4 administration of the vitamin B preparation was begun. The symptoms became ameliorated with the exception of abnormal motility and atrophy. About the middle of March, the heart was distinctly smaller; the area of absolute dulness extended from the midline to the lower edge of the fourth rib and one and one-half fingerbreadths inside the nipple line. Abnormalities of the heart sounds were not present. The patient could take a few steps without being supported. He had regained some strength in his legs, but they were still weak. On March 23 the patient suffered from inflammation of the colon and sigmoid with purulent, mucous and somewhat bloody diarrhea and tenesmus with colicky pain. On May 28 he left the hospital with marked amelioration of symptoms.

The average basal metabolism during the time that the patient was on his usual diet was + 1.5 per cent; during vitamin B starvation it was — 3.5 per cent, and with vitamin B medication or when the usual diet was resumed, it was + 5.6 per cent.

CASES 8 and 9.—As symptoms did not develop, the protocols of these cases are omitted.

Comparing the protocols of the aforementioned five cases (cases 5 to 9) with the observations of the basal metabolism, we note that in the three cases in which typical symptoms of avitaminosis developed,

TABLE 8.—*Metabolism Data on Healthy Patient (Case 8*)*

Date, 1925	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication of the Previous Day
1/23	45.2	1.34	58	12	0.67	36.7	— 7.1	36.2	Usual diet
1/24	45.2	1.34	58	13	0.81	42.1	+ 6.6	36.4	Usual diet
1/25	45.6	1.35	56	13	0.76	39.6	+ 0.2	36.6	Usual diet
1/26	45.3	1.34	54	13	0.75	42.1	+ 6.6	36.3	Usual diet
2/ 4	46.7	1.36	57	14	0.77	42.4	+ 7.2	36.6	Restricted diet 7 days
2/13	47.3	1.37	61	12	0.80	43.7	+10.7	36.1	Restricted diet 16 days
2/18	47.3	1.37	62	12	0.72	44.9	+13.7	36.4	Restricted diet 21 days
2/20	47.4	1.37	62	12	0.86	40.6	+ 2.7	36.4	Restricted diet 23 days
2/23	47.4	1.37	58	12	0.80	43.2	+ 9.2	36.6	Restricted diet 26 days
2/27	48.2	1.38	62	12	0.83	41.2	+ 4.3	36.4	Restricted diet 30 days
3/ 3	48.1	1.38	60	11	0.85	40.7	+ 3.0	36.8	Restricted diet 34 days
3/11	48.8	1.39	71	13	0.80	42.6	+ 7.9	36.5	Restricted diet 42 days
3/16	48.8	1.39	..	10	0.85	39.8	+ 0.6	36.4	Restricted diet 47 days
3/20	49.2	1.39	62	11	0.74	42.0	+ 6.3	36.6	Restricted diet 51 days
3/27	47.6	1.37	72	12	0.83	43.4	+ 9.8	36.2	Restricted diet 58 days
3/30	50.0	1.40	72	15	0.87	42.9	+ 8.5	36.5	Restricted diet 61 days
4/ 4	50.4	1.41	68	12	0.80	45.0	+13.9	36.8	Restricted diet 66 days
4/10	51.6	1.41	75	14	0.94	45.2	+14.4	36.4	Restricted diet 72 days
4/13	51.1	1.41	82	14	0.84	41.9	+ 6.2	36.5	Restricted diet 75 days

* Z. A., man, aged 20, 145.5 cm. in height.

TABLE 9.—*Metabolism Data on Healthy Patient (Case 9*)*

Date, 1925	Weight in Kg.	Body-Surface (Du-Bois)	Pulse Rate	Respiration Rate	Respiratory Quotient	Calories per Sq. Meter per Hr.	Basal Metabolic Rate (Du-Bois)	Temperature, C.	Diet and Medication
1/28	54.3	1.56	70	15	0.81	38.6	— 2.2	36.1	Usual diet
1/29	55.1	1.57	67	13	0.74	44.1	+11.6	35.6	Restricted diet 1 day
1/30	55.3	1.58	65	12	0.72	44.1	+11.6	36.0	Restricted diet 2 days
2/ 6	54.9	1.57	58	12	0.80	39.4	— 0.2	35.9	Restricted diet 9 days
2/ 7	55.2	1.57	59	12	0.80	39.8	+ 0.6	35.9	Restricted diet 10 days
2/13	55.2	1.57	62	12	0.87	40.1	+ 1.4	35.8	Restricted diet 16 days
2/14	54.7	1.57	62	11	0.72	39.7	+ 0.4	35.3	Restricted diet 17 days
2/18	55.0	1.57	62	11	0.83	36.7	— 7.1	35.4	Restricted diet 21 days
2/20	55.1	1.57	59	12	0.84	38.3	— 3.0	35.6	Restricted diet 23 days
2/23	54.6	1.57	56	14	0.79	41.6	+ 5 3	35.6	Restricted diet 26 days
2/27	55.1	1.57	62	12	0.77	40.2	+ 1.7	35.9	Restricted diet 30 days
3/ 2	54.5	1.57	56	11	0.82	35.1	—11.1	35.8	Restricted diet 33 days
3/ 6	55.1	1.57	78	13	0.81	41.0	+ 3.8	36.1	Restricted diet 37 days
3/16	55.0	1.57	63	10	0.83	37.8	— 4.3	35.4	Restricted diet 47 days
3/20	54.4	1.57	65	11	0.71	42.7	+ 7.8	36.2	Restricted diet 51 days
3/23	54.8	1.57	63	12	0.76	40.2	+ 1.7	35.8	Restricted diet 54 days
3/27	55.2	1.57	68	12	0.72	44.8	+13.4	35.8	Restricted diet 58 days
4/ 4	55.3	1.58	66	11	0.83	37.6	— 4.7	35.9	Restricted diet 66 days
4/10	55.6	1.58	72	11	0.86	43.2	+ 9.3	35.8	Restricted diet 73 days
4/13	55.6	1.58	64	9	0.81	43.7	+10.7	35.8	Restricted diet 76 days
4/17	56.1	1.58	69	12	0.82	39.0	— 1.4	35.9	Restricted diet 80 days
4/20	55.9	1.58	66	12	0.74	40.3	+ 2.0	35.8	Restricted diet 83 days
4/24	55.9	1.58	64	15	0.70	36.3	— 8.0	35.9	Restricted diet 87 days
4/30	56.1	1.59	72	13	0.85	41.1	+ 4.5	35.9	Restricted diet 93 days
5/ 3	55.9	1.58	65	14	0.83	36.6	— 7.4	35.8	Restricted diet 96 days
5/ 9	55.9	1.58	57	14	0.80	40.6	+ 2.8	35.8	Restricted diet 102 days
5/13	55.9	1.58	68	14	0.77	37.1	— 6.1	35.8	Restricted diet 106 days
5/18	55.8	1.58	64	16	0.79	33.6	—15.0	36.0	Restricted diet 111 days
5/22	55.4	1.58	64	14	0.79	39.0	—26.5	36.0	Restricted diet 115 days
5/27	55.9	1.58	64	14	0.64	31.2	—21.1	35.9	Restricted diet 120 days
6/ 1	54.5	1.57	68	15	0.76	41.0	+ 4.1	35.9	Usual diet 2 days
6/ 5	54.9	1.57	59	15	0.73	34.1	—13.8	36.0	Usual diet 6 days

* H. F., man, aged 20, 161.3 cm. in height.

† From May 7, the restricted diet was boiled twice.

there was more or less decrease in the basal metabolism (the average decrease during the avitaminous alimentation being 12.1 per cent, 9.4 per cent and 5 per cent); while in two cases, in which observations were made for a long time and in which no symptoms developed, there was no change in the basal metabolism except during the last period in the last case (case 9), after administration of twice boiled accessory food, serious distaste for the food and indigestion occurred, and the intake of food was highly reduced. Especially interesting is case 5, in which the prescribed food was always eaten until the end of the experiment. The basal metabolism in this case had been typically reduced, remarkably at the beginning of the development of the symptoms and rising somewhat during the latter period, parallel with the increase in the pulse rate. Vitamin B medication caused increased metabolism. In case 6 a low rate of metabolism still continued after administration of the vitamin B preparation. It is difficult to explain this; we shall only mention that the intake of food, especially on the previous day of determination of the basal metabolism, was sufficient, although the patient had not recovered his appetite, and a slight paralysis of the legs was present (when paralysis exists, increase in the basal metabolism is usually postponed). After the administration of the vitamin B, however, the basal metabolism gradually returned to the original value, with amelioration of the symptoms. In case 7 there was also a slight decrease in the basal metabolism with the beginning of the symptoms, but the change in this case was not so remarkable as in other cases, perhaps because an increase in the pulse rate appeared relatively early. After resuming the usual diet, the basal metabolism again became increased (the average pulse rate at the time of determination of the basal metabolism during vitamin B starvation was 62 in case 5, 60 in case 6 and 78 in case 7).

COMMENT

The first series of experiments showed that vitamin B starvation causes an aggravation of symptoms of beriberi and a marked decrease in the rate of basal metabolism. After administration of a vitamin B preparation, the symptoms were ameliorated, and the basal metabolism resumed its original value. The second series of experiments showed that by means of a long continued diet deficient in vitamin B, typical symptoms of avitaminosis develop, and the rate of basal metabolism decreases, especially at the initial symptoms, increasing somewhat with the involvement of the cardiovascular system (increase of the pulse). The decrease in basal metabolism in the second series was not so remarkable as in the first series of experiments, which probably is due to the degree of the deficiency of vitamin B in the diet. If the deficiency of vitamin B is slight, no symptoms develop, and the basal metabolism

shows almost no change, as in cases 8 and 9. From these results it may be concluded that vitamin B starvation without general starvation causes a decrease in the basal metabolism; in beriberi it causes an aggravation of the disease; in healthy persons typical symptoms of avitaminosis develop after an incubation. The decrease in the basal metabolism is especially significant just at the beginning of the symptoms, becoming less significant later, parallel with the increase in the pulse rate. In both series the symptoms are ameliorated after the administration of vitamin B. From these observations it seems plausible that the deficiency in vitamin B has some special relation to the exacerbation or aggravation of beriberi.

It seems important to consider whether beriberi and avitaminosis are one and the same disease or two different diseases with some similar symptoms. This problem has already been enthusiastically discussed by many investigators, but is not yet definitely solved. We have not tried to survey the literature for a solution to this problem, as results are too numerous and contradictory and too far from our main purpose. We found that in beriberi the basal metabolic rate is usually normal, and when cardiovascular involvement becomes significant, it is increased; when paralysis occurs, the rate decreased. Our experiments show that there is a definite decrease in basal metabolism in the course of vitamin B starvation, so that it seems probable at first that beriberi and avitaminosis are essentially two different diseases. However, the decrease in basal metabolism during vitamin B starvation is especially significant at an early period of avitaminous manifestation followed by an increase nearly parallel with the increase in the pulse rate. In view of the fact that most investigators never recognized the resemblance of the remarkable cardiovascular symptoms in avitaminosis to those in beriberi until now, the difference in observations in the basal metabolism must be used cautiously in the differentiation of these two diseases. Observations on the basal metabolism by some of the leading research workers on beriberi in Japan have shown that there are still many factors in these two diseases which are different; therefore we cannot yet say definitely whether beriberi and avitaminosis are two diseases or the same disease. It is possible also that in addition to the avitaminous state some other important factor is necessary to account for the manifestation of true beriberi.

SUMMARY AND CONCLUSIONS

1. Vitamin B starvation in patients with beriberi causes aggravation of the symptoms and a decrease in the basal metabolism. Administration of a vitamin B preparation ameliorates the symptoms and increases the rate of basal metabolism.

2. Prolonged vitamin B insufficiency in healthy persons causes typical avitaminosis and decrease in the rate of basal metabolism, especially at the beginning of the manifestation of symptoms. Administration of a vitamin B preparation cures the symptoms and increases the rate of basal metabolism.

3. The identification of beriberi with avitaminosis is difficult at present as there are many factors in these two diseases which are not similar. According to the observations on the basal metabolism, the diseases do not coincide. In beriberi we usually found that the basal metabolism was normal. When decompensation was threatened, there was an increase in the rate, and when paralysis and atrophy were present, there was a decrease. In avitaminosis we always found a decrease in the basal metabolism, especially at the beginning of the exacerbation of the symptoms. A serious involvement of the cardiovascular system in avitaminosis which possibly causes an elevation of the rate of basal metabolism was not observed. We know that when the pulse rate increases in the course of avitaminosis, an increase in the rate of basal metabolism follows. Therefore it is difficult to decide without further investigation whether or not this divergence in the metabolic observations has an essential value for the differentiation of these two diseases.

(The clinical observation and other investigations of the avitaminosis experiment were performed by Professor Inada, Drs. Mozai, Tanino, Akiya, Horiuchi, Ohta and Donomae).

EXOPHTHALMIC GOITER AND THE INVOLUNTARY NERVOUS SYSTEM

XIII. THE COURSE OF THE SUBJECTIVE AND OBJECTIVE MANIFESTATIONS OF EXOPHTHALMIC GOITER IN FIFTY UNSELECTED PATIENTS. OBSERVATIONS FOR FIVE YEARS WITHOUT INSTITUTION OF "SPECIFIC" THERAPEUTIC MEASURES ("SPONTANEOUS COURSE")*

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In a previous article [1] on exophthalmic goiter and the involuntary nervous system, we have recorded our observations on fifty unselected patients studied for two years. The following excerpt taken from this article will explain the system we followed in making our observations.

In January, 1921, we instituted a study of fifty unselected cases of fully developed exophthalmic goiter.[2] No specific therapeutic measures were employed "in order to determine the natural history (spontaneous course) of the disease," [3] and to establish an "index for the evaluation of therapeutic procedures." [4] From the group were excluded (*a*) patients who had thyroid enlargement without other manifestations of exophthalmic goiter,[5] and (*b*) those who, with or without thyroid enlargement, presented sympathomimetic symptoms, without significant elevation of the basal metabolism (autonomic imbalance).[6] In the group studied, we included (1) patients with a significant elevation of metabolism on repeated readings; (2) patients whose illness was sufficiently severe to warrant residence in a hospital where beds are at a great premium (two exceptions), and (3) patients from the poorest sections of the city, who were subjected to constant economic strain (one exception).

The patients were first observed in the general wards of the hospital. An attempt was made to secure for them complete physical and mental relaxation. A high caloric diet (3,000 calories) was ordered and wet packs at 75 degrees were used daily. In the beginning, daily colon irrigations were employed, but these were later discontinued. Foci of infection, particularly in the nose and

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throat were attacked, and extirpated or drained. Phenobarbital (luminal), 1½ grains, was used as a hypnotic and syrup of ferrous iodid, from 5 to 30 minims, three times a day, was prescribed to hasten the involution of the thyroid.[7]

After an average hospital stay of six weeks, the patients were sent to the country, and were given small tasks. In another two to six weeks, they were returned home, and permitted to resume their responsibilities gradually. They were instructed as to their disease and were warned that the condition was arrested rather than cured and the possibility of recurrence was emphasized. They were urged, in addition to regular attendance at the out-patient department, to return at the recurrence of the slightest symptoms. The families were warned that these people must be protected, but without coddling. All the follow-up observations were made personally by us. In our presentation, we included a history of these fifty consecutive patients, irrespective of end-results, and with extensive follow-up observations. When the patient could not be kept under observation, we regarded the issue as unsuccessful.

In this paper, we present the subjective and objective results at the conclusion of a period averaging fifty-eight months, including all data to Jan. 1, 1927.

SUBGROUPING OF PATIENTS

A. *Fatalities.*—Eight deaths have occurred, of which one, due to a carcinoma of the stomach, is excluded from the statistical study. The remaining seven deaths may be summarized as follows: cardiac failure, two; infection, one; status lymphaticus, one; thyrotoxicosis, two, and thyroidectomy, one. Five of these deaths have been discussed previously.[6] Since this report was made, two patients, elderly women, have died of cardiac failure due to exophthalmic goiter. In addition, one had severe diabetes mellitus, and the other a superimposed subacute bacterial endocarditis. They would have been desperate operative risks even when first admitted to our service.

B. *Patients Who Sought Specific Therapy.*—Ten patients considered their progress unsatisfactory, and sought some type of specific therapy. We regard these as "failures" from our standpoint. One patient (B. A. W.) received treatment from an endocrinologist. We have been unable to obtain complete records from her or from her physician. Another, (D. H.) received radium therapy, with what appears to be an excellent result. This is the only noteworthy result of radium therapy that we have observed.

7. "1. Almost without exception, no patient in this series received iodid during the first month of observation and rarely within the first six weeks, during which time the greatest improvements were noted. 2. The administration of the iodids was not accompanied by any marked alteration in the rate of improvement in our experience: when benefit accompanied the exhibition of the drug, it was unusual to observe any changes other than a continuation of the amelioration of symptoms noted in the preceding weeks." There was no other routine medication. No purposeful psychotherapy was employed, but the patients were shielded, as far as possible, from psychic trauma, and attempts were made to adjust their social and economic difficulties.

The remaining eight patients were subjected to a subtotal thyroidectomy, either at our institution or elsewhere, and we have fortunately been able to follow most of them throughout their course.

One man (M. F., referred to in section A) died immediately following operation. The operative mortality in this group is therefore 12.5 per cent.

One patient (D. J.) made good progress. We had observed her for two years of relatively uncomplicated convalescence, and then, following an automobile accident, an exacerbation ensued. When the patient was treated with a compound solution of iodine and rested in bed, the basal metabolic rate fell from plus 65 to plus 24 per cent. Dr. Moschcowitz then performed a subtotal thyroidectomy, which was followed by a severe and prolonged postoperative reaction. The patient was discharged on the fifteenth day after operation, with a normal basal metabolic rate, and in the two years that have elapsed she has gained 34 pounds (15.4 Kg.). Though she has gone through a pregnancy, the basal metabolic rate and the pulse rate are normal. The exophthalmos is unchanged.

We regard the results in three cases as good, but not particularly brilliant. One of these patients (R. B.) was given roentgen-ray therapy at the Roosevelt Hospital, and then a ligation was performed in October, 1922. At a second admission, two months later, a partial thyroidectomy was performed, with a resultant fall in the basal metabolic rate from plus 43 to plus 6 per cent, and a gain of 21 pounds (9.5 Kg.). At the third admission, in October, 1924, another partial thyroidectomy was performed, following which the patient was admitted to the Memorial Hospital, where a diagnosis of carcinoma of the parotid was made by Dr. Coley. Six months later, however, we heard that the patient was doing fairly well. We have not been able to complete our records in this case. Another patient (B. R.) has been relieved of attacks of paroxysmal cardiac irregularity since thyroidectomy was performed, though the operation was followed by aphonia from paralysis of the cord. Finally, a young girl (G. D.) was observed by us for thirty months, and then had a partial thyroidectomy performed by Dr. Emil Goetsch in October, 1923, after four roentgen-ray treatments. The basal metabolic rate before operation was only minus 3 per cent. The patient was in the hospital for ten days, and most of the right lobe and isthmus were removed. She has as residual symptoms a tachycardia of 100, an exophthalmos of 23-23, and hyperplasia of the thyroid remnant, but she is considerably better than at any time prior to operation, and able to fill a difficult position.

Three operative results are indeterminate. One woman (M. H.) was symptom-free at the time of operation. Another woman (N. J.), after a stormy period under our care, had a ligation performed by

Dr. Crile, in August, 1923, which was followed by a severe reaction. A second ligation was performed on September 2, and two months later a subtotal thyroidectomy; this was followed by dysphonia from paralysis of the cord. For the next eight months her nervousness, irritability, asthenia, palpitation and tremor were unimproved, and at rest she had a pulse rate of 116. She went home to New Zealand, improving considerably during the ocean trip, and when we saw her two years after operation, she was much better but by no means well. One patient (L. R.) had a partial thyroidectomy performed by Dr. John Erdmann in June, 1923. Eight months later she was improved, but still complained of nervousness, tremor and palpitation. Her exophthalmos measured 20-20, the thyroid remnant had undergone a compensatory hyperplasia, she had a tremor and a pulse rate during examination of 136. Nine months after this, she was considerably improved. Her basal metabolic rate was normal, and for another six months her progress was satisfactory. Then she had a recurrence of an old sinus infection, which resulted in an exacerbation of symptoms, and she went to Dr. Crile, who completed the thyroidectomy in September, 1926. We saw her two months following operation, and, while she was still weak, she was somewhat improved; her pulse rate was 78, and she had gained 10 pounds (4.5 Kg.) The exophthalmos was unchanged. It is too soon to estimate the value of the operative procedure.

In addition to these eight, six of our patients had had operative treatment before they came to us. In every one of these six instances, the symptoms had recurred with sufficient intensity to incapacitate the patient. Of the six, one (L. K.) died of a status lymphaticus fourteen years after subtotal thyroidectomy was performed. Partial thyroidectomy was performed on three patients and simple ligations on two, with unfavorable results.

C. *Patients Lost from Observation*.—Three patients were lost from observation. Two were doing poorly when we last saw them (E. N. and S. S.) One man (J. W.) was doing well when last seen.

D. *Patients Successfully Followed*.—Thirty-one patients have been successfully followed, twenty-five for more than four and a half years and fourteen for over five years. We shall analyze the progress of these thirty-one persons.

1. Subjective Symptoms: It is difficult to present and interpret the subjective symptoms of patients with exophthalmic goiter. A few generalizations can be made. The subjective symptoms did not entirely disappear in any of our patients. The subjective symptoms do not bear a constant relation to the intensity of the disease, to the basal metabolic rate or to the economic restitution of the patient. Asthenia,

nervousness, insomnia and palpitation are symptoms particularly prone to persist or to recur on slight provocation. Economic restitution is by no means analogous to freedom from subjective complaints. As a general rule, however, it is fair to say that the subjective symptoms in these patients have strikingly and markedly diminished.

2. Objective Observations: (*a*) Exophthalmos. The right hand columns in chart 3 indicate the first and the last exophthalmometer readings. The last reading averages five years after the first. Thirteen of the twenty-four completed records do not show appreciable change. Seven have decreased slightly, and four have increased. The other eye signs in exophthalmic goiter are subject to individual variation, and are lacking in value because such signs as von Graefe's, particularly, may be observed in persons without exophthalmic goiter. We urge exophthalmometer readings as a routine measure, for they are the only accurate gage of the eye signs.

(*b*) Pulse Rate. The pulse readings obtained in a follow-up clinic are subject to so many modifications that they are impossible to interpret with any degree of accuracy, and our observations on pulse rate are therefore of little value. The basal pulse should be recorded in exophthalmic goiter, and usually parallels the basal metabolic rate. In order to obtain the basal pulse rate, the same elaborate precautions which are necessary in estimating the basal metabolic rate should be exercised, and this we have not been able to do in a follow-up clinic. Therefore, we prefer to omit our observations on the pulse rate, rather than to report grossly inaccurate figures. All of our patients retained a lability of the pulse rate, and it was exceptional to record a rate of below 80, even when the basal metabolic rate was normal and the patient symptom-free.

(*c*) Tremor. Many of these patients retain a fine tremor, visible only on examination of the outstretched fingers. In no instance was the tremor complained of subjectively or was it of sufficient intensity to interfere with the patient's occupation.

(*d*) Goiter. In no instance did the goiter completely disappear, though in four patients it was noticeable only to the examiner. Any attempt to classify these patients according to the anatomic appearance of the goiter was unsuccessful. While patients could be distinctly classified clinically, as has been pointed out by many writers,[8] this classification could not be correlated with the alterations in the thyroid gland.[9] In presenting another group of patients, in which the opportunity of making histologic studies was afforded, this point will be dealt with more fully.

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8. Plummer, H.: Tr. A. Am. Phys. 1916, p. 138.

9. Graham, Allen: Exophthalmic Goiter and Toxic Adenoma, J. A. M. A. **87**:628, (Aug. 28) 1926.

(*c*) Basal Metabolic Rate.[10] The course of the basal metabolic rate is recorded graphically in chart 2, and the individual records appear in chart 1. In chart 1 the first line of figures represents the basal metabolic rate on admission, and at six and twelve months are recorded the readings which occurred nearest to that period. Naturally, many readings were made in the first few weeks, during the course of the hospital stay, and all of these are omitted from this chart, but they appear in a previous paper.[1] After the twelfth month all the readings are recorded, for these have not hitherto appeared, and they give an excellent idea of the progress of the patient.

From chart 2 it will be seen that at the end of six months the average basal metabolic rate, which on admission was plus 43 per cent, had fallen to plus 22 per cent, and at the twelfth month to plus 17 per cent. The fall continues at two and three years to plus 14 and plus 10 per cent.

In the fourth year, there is a slight rise, due to four high readings that occurred in the patients. In the forty-eighth month, in patient 1, a basal metabolic rate of plus 39 per cent is recorded, following a serious accident to her son. In patient 9, also at the forty-eighth month, a basal metabolic rate of plus 50 per cent is recorded, as a result of a purulent pansinusitis. In patient 22, two high readings are recorded, of plus 34 per cent and plus 53 per cent, and these occurred while the patient was gaining 40 pounds (18.1 Kg.) over her weight on admission. She is an extremely stupid person, and we have never been able to secure her cooperation during the basal metabolism test. We are therefore more inclined to believe that this reading is not basal.[11] But one other reading of over plus 17 per cent occurred, and the average of the remaining readings is plus 8 per cent.

In the fifth and sixth years slight rises are observed, the average being plus 17 per cent in the fifth year, and plus 19 per cent in the sixth year. These rises again are due to individual elevations. Thus, plus 49 per cent in the third patient on the list was recorded during an attack of paroxysmal flutter just prior to her marriage. Sixteen months later, her basal metabolic rate was found to be plus 12 per cent. Again, in patient 5, a plus 40 per cent is recorded in the sixty-third month, at a time when her husband was out of work, and she was suffering great privation and was overworking. During this period, and

10. The readings of the basal metabolic rate have been made on the Roth-Collins machine by Dr. Herman Lande and his assistant, Miss A. K. Steiner.

11. Since the writing of this article, we were fortunately able to secure another basal metabolic rate on this patient on Jan. 18, 1927, when, with adequate cooperation from the patient, her rate was recorded at plus 17 per cent.

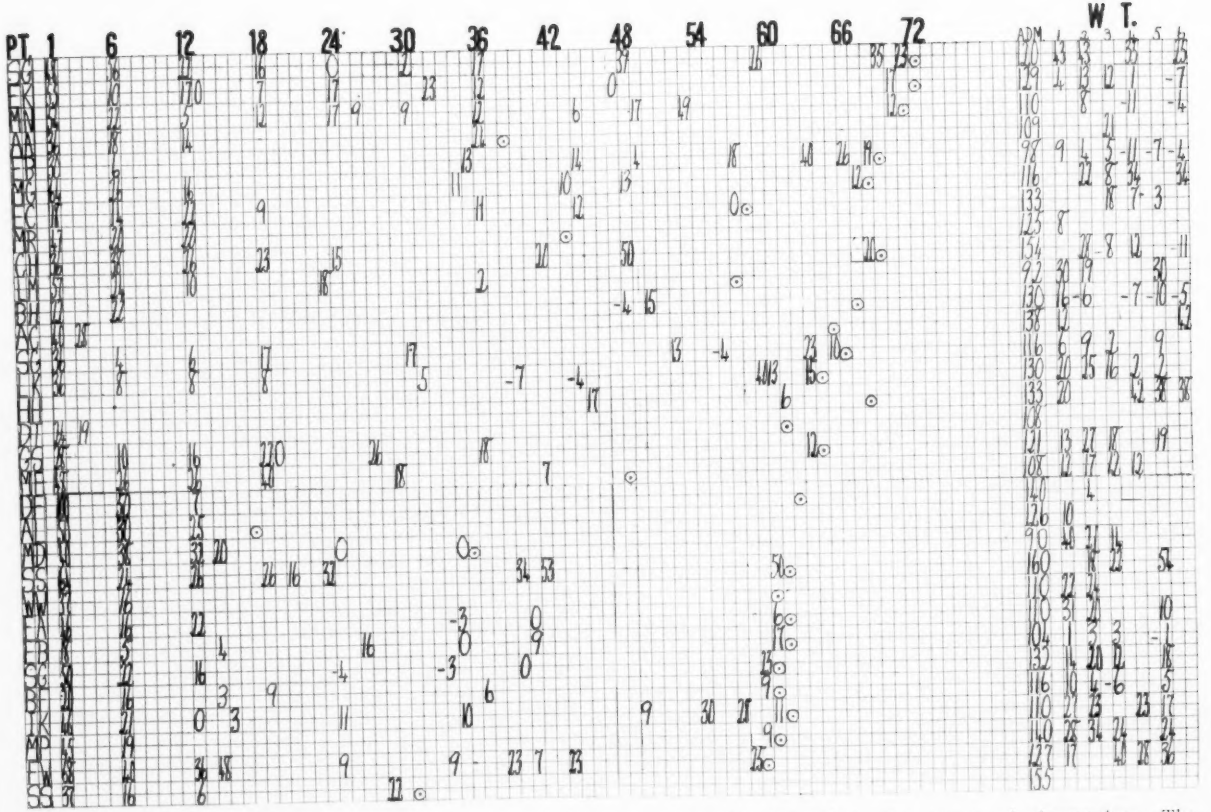

Chart 1.—The individual record of the basal metabolic rate and weight throughout the course of observation. The first figure gives the basal metabolic rate on entrance. The figure at six months is the nearest reading to that time. All the intermediate readings are omitted, but appear in article X (Arch. Surg. 8:149 [Jan.] 1924). After the sixth month all readings are included. The dot with the circle around it indicates the time of the last visit. The weights at the various years are given in reference to the weight at admission and are not cumulative.

despite the elevation of her basal metabolic rate, she was working from 6 in the morning until between 10 and 11 at night, as janitress in a tenement house, in addition to taking care of her household. In the sixty-eighth month, her rate had fallen to a plus 19 per cent. During this period, she was not at any time economically incapacitated. Again, a plus 40 per cent is recorded in the fourteenth patient in the fifty-ninth month. This occurred simultaneously with a miscarriage, and a month later, following a curetage, the rate fell to plus 13 per cent. A rate of plus 50 per cent is recorded in patient 22, to whom reference has already been made. If these readings are omitted, the average reading would have been 13 per cent in the fifth year and 17 per cent in the sixth year.

It should be understood that all readings were taken while the patients were ambulatory, so that they are, if anything, slightly higher than would be obtained in patients who were in bed. Many of our patients who were progressing satisfactorily could not leave their work to come to the hospital for metabolic readings. An example of this is patient 10, who had a rate of minus 2 per cent in her thirty-sixth month and who, owing to her work, was unable to report for a basal metabolic reading thereafter.[12] A reading has not been made for patient 16 since her third month. This patient lives out of town, and we hear from her only by letter. Patient 19, who had a basal metabolic rate of plus 7 per cent at one year, has not been able to come for a reading since, though we are still in communication with her at the sixty-second month. She has just had another baby, and cannot leave it to come to the hospital. Patient 23, whose last reading was a plus 16 per cent in the sixth month, lives out of town, and writes to us that he does not have any symptoms referrable to exophthalmic goiter. Had these patients been able to call on us, the average basal metabolic rate would have been materially lowered.

The basal metabolic rate that reached normal in the twelfth month, has remained well within normal limits throughout the following five years.

Nineteen readings of zero or an actual minus will be seen, contrary to the usual statement that these patients do not reach normal or subnormal readings unless they are the subjects of specific therapy. None of these patients presented any clinical evidences of myxedema.

(*f*) Weight. The weights are recorded in chart 1. The graphic chart shows an increase of 18 pounds (8.2 Kg.) in the first and second year, and, though this gain was not completely held in the succeeding years, the patients did maintain an average gain of 11, 12 and 13 pounds

12. Since the writing of this article, the patient has reported for observation, and her basal metabolic rate is plus 4 per cent in the fifty-ninth month.

first figure gives the basal metabolic rate on entrance. The figure at six months is the nearest reading to that time. All the intermediate readings are omitted, but appear in article X (Arch. Surg. 8:149 [Jan.] 1924). After the sixth month all readings given in reference to the weight are indicated as the time of the last visit. The weights at the various

(5, 5.4 and 5.9 Kg.) in the third, fourth and fifth years, respectively. The record of the weight of each patient will be seen to the right of chart 1, the first column being the weight on admission, and the readings in the other columns show the loss or gain during the various years. Loss of weight is indicated with a minus sign; if no sign occurs, there is a gain. These figures are not cumulative, but each figure is with reference to the admission weight in the left hand column.

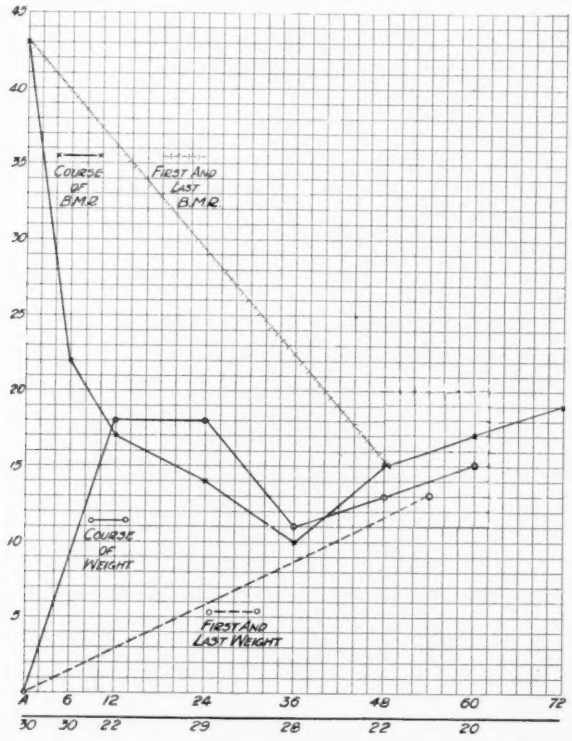

Chart 2.—The course of the weight and basal metabolic rate in exophthalmic goiter. The first and last basal metabolic rate and weights are compiled from the entrance figures and the last figures available, and the time is the average of the last observations. The course of the weight and basal metabolic rate is based on all available readings after the sixth month, and the figures at the bottom indicate the number of readings on which the final readings was based. The individual readings will be seen on chart 1.

A few comments on the patients may be of more than passing interest. In the first year, nine patients gained 20 pounds (9 Kg.) or more. In only one patient has a loss of weight occurred in the first two years. In the third year, two losses in weight occurred, one in the

same patient in whom it occurred during the second year. At the end of six years, six patients show a loss in weight, and twenty-five have gained weight, the average difference in weight between the first and last weight being 14 pounds (6.4 Kg.). One patient has gained over 50 pounds (22.7 Kg.), and this patient, curiously enough, is the one who had a plus 50 per cent metabolism in her sixtieth month, and a plus 53 per cent in her forty-first month; we have commented already on this patient. Five patients have gained 30 pounds (13.6 Kg.) or more, and four more between 20 and 30 pounds, so that ten of the twenty-six patients have gained more than 20 pounds in the course of the six years.

Of the six who lost weight, one has lost 1 pound (0.5 Kg.); one, 5 pounds (2.3 Kg.); one, 7 pounds (3.2 Kg.), and two have lost 4 pounds (1.8 Kg.). One woman has lost 11 pounds; she is the patient with the recurrent pansinusitis.

(*g*) Social and Economic Restitution. Social and economic restitution is the most important desideratum from the standpoint of the patient, and may be independent of any of the subjective and objective manifestations. In this group (chart 3), there is an average period of hospitalization (full shading) of six weeks and an average period of rest in the country (three-fourths shading) of five weeks, which is followed by variable periods of rest at home (half shading). By the third month fifteen, or over half, were restored; by the sixth month, all but three patients were economically restored. Of the three patients who had a prolonged convalescence, one (A. C.) was a malingerer and another (A. L.) was an old woman with essentially abdominal symptoms, due to a cholecystitis. The third was a young girl (M. D.), who, despite the prolonged period of convalescence, has made favorable progress since. During the remainder of the period of observation, little or no economic and social incapacitation has occurred, as will be seen by an almost complete absence of shaded portions. Eight periods of incapacitation, due to some disease other than exophthalmic goiter (hatching), have occurred. In most instances these were due to a tonsillectomy (*T*) or to an infection of the upper respiratory tract (*I*). In only one instance did a true exacerbation occur; in the third patient's fifty-third month, a mild exacerbation developed and was accompanied by a paroxysmal flutter prior to marriage.

Worthy of comment, too, is the number of pregnancies that have occurred. Eight of the patients have borne twelve normal children, without exacerbation of symptoms, and the pregnancy, labor and children have all been normal. The test of labor was adequately met in all instances.[13]

13. The majority of these patients were delivered by Dr. C. F. Jellinghaus at the Lying-In Hospital in New York.

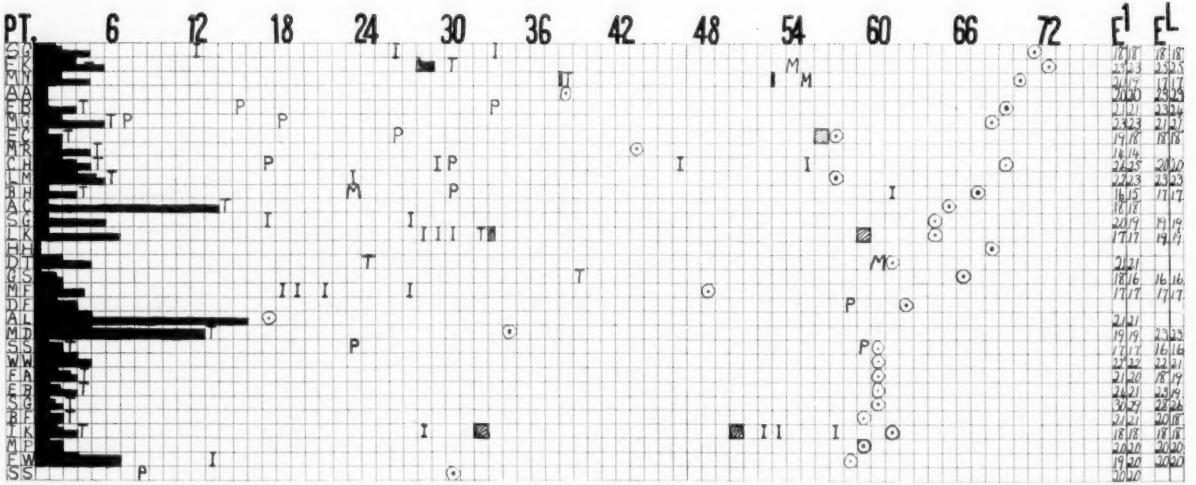

Chart 3.—The course of the disease with regard to social and economic incapacitation. The patients are listed in the same order as in chart 1. Full shading indicates hospitalization; three-quarter shading, rest in the country; half shading, rest at home; hatching indicates incapacitation due to some disease other than exophthalmic goiter. When no shading occurs, the patient is socially and economically restored. *I* indicates infection, usually of all the upper respiratory tract; *T*, tonsillectomy; *P*, pregnancy; *M*, marriage. The time of the last observation is again indicated by a dot with a circle around it. The exophthalmometer readings are the first and last for each eye.

Economic restitution occurred for an average of fifty-two months in the fifty-seven months' average span of observation in this group. The average time for social and economic restitution was four and a half months, and during the remaining fifty-two and a half months these people were able to assume their burden as wage-earners or housewives in the trying circumstances of metropolitan life. They all had residual symptoms, usually negligible, sometimes annoying, but never sufficient to cause them to go to bed, partially due to the fact that a day or even a few hours in bed among this class of patients is far too great a luxury. Doubtless the same symptoms in the more leisurely walks of life would have resulted in variable periods of incapacitation. At times the recurrence of the symptoms was associated with elevation of the basal metabolic rate and loss of weight, but in only one instance was this sufficient to compel the patient to seek hospitalization.

It would be wrong to give the impression that this period was as free from difficulty as the chart would make it appear. Difficulties and symptoms of one type or another were constantly present, but the important fact is that none of these difficulties or symptoms were sufficient to result in the patient's being economically incapacitated.

(*h*) Complications and Associated Diseases. Among the associated conditions, the most common were tonsillar and upper respiratory infections. Both of these bear an etiologic relationship to the disease, as we have previously indicated.[1] Tonsillectomy was performed on twenty-four of the patients—on ten under local and on fourteen under general anesthesia. We observed no unusual reactions to the tonsillectomy, except that in one instance a patient suffered a severe and prolonged sympathomimetic sensitization from the procaine hydrochloride. The choice of anesthesia is still a matter for discussion.

A number of patients suffered from intercurrent and unassociated conditions, such as chronic bronchitis, gynecologic disturbances, cholelithiasis, asthma and infectious arthritis.

The alleged degenerative changes have not occurred in these patients with any degree of regularity. Two men have hypertension, and have had it all these years without alteration in the heart or kidneys. We are under the impression that the hypertension is more apparent than real, and varies in these patients with the same lability as the pulse rate. Three women have had attacks of cardiac irregularity on provocation; in all, the irregularity has subsided and has not recurred.

(*i*) Subgroupings. The clinical picture of exophthalmic goiter is rarely typical, and generally no two patients present the identical syndrome. Two large subdivisions are clearly to be noted, as was first pointed out by Plummer. These subdivisions are characterized most

clearly by the exophthalmos in the one group and by little or no exophthalmos in the other. Usually, the group without exophthalmos are older and the symptoms are of longer duration; more often there are cardiac symptoms. We clearly recognize these subdivisions, but that the differences in the two groups are due to any histologic alteration in the thyroid, such as the presence or absence of adenomas, or to any alleged change in the secretion of the thyroid, seems to us to be an unwarranted conclusion, for reasons to be discussed more completely in another place. Of our thirty-one patients here listed, twenty-four would be included in the exophthalmic group and seven in the nonexophthalmic group; of the remaining nineteen patients, seven would be included in the nonexophthalmic group and of these four died. The percentage of deaths in the nonexophthalmic group is therefore considerably higher than in the other group, so that these patients are clearly more liable to cardiac complications, infections and fatal thyrotoxicoses. The explanation for this, to us at least, is not patent. Of the patients who sought specific therapy, nine were in the exophthalmic group, and of those lost from observation, one was in the exophthalmic group, so that in the nonfatal cases which we regard as failures, three were in the nonexophthalmic group and ten in the exophthalmic group. From this small series of observations we can simply say that if the two subdivisions are recognized, patients in the nonexophthalmic group are seen less frequently, are more prone to fatal or incapacitating complications, and usually are older women. The fact that these people have adenomas in their gland by no means proves that the adenomas are the cause of the alteration in the clinical picture, for they may occur much more commonly in patients without symptoms; they may also occur in patients with the exophthalmic type of the disease or in myxedema. This attempt to classify clinical material on pathologic changes in the thyroid suffers from the same weakness as the now neglected theory that pathologic hyperplasia of the thyroid is indicative of a physiologic hypersecretion, a theory as strongly urged and with as little actual demonstration as the present theory of the toxicity of adenomas.

SUMMARY

The facts concerning the spontaneous course of exophthalmic goiter are presented baldly, with a minimum of comment, and without effort to evaluate specific methods of therapy. This presentation is made for the purpose of establishing a norm or control, and not for the purpose of outlining a therapeutic policy. Later we shall report our results with various types of specific therapy, and, having so done, we shall make an attempt to discuss therapeutic policies Our purpose is the collection of data, and not an attempt to prove or disprove theories or points of view. Of the fifty patients, the spontaneous course was followed in thirty-one; of the nineteen whose spontaneous course could not be completed, six

died (a mortality of 12 per cent) and thirteen were either lost from observation or received specific therapy. Of the latter, two received nonoperative therapy, and eight operative therapy; one of the eight died, making operative mortality in this group of 12.5 per cent.

With regard to the spontaneous course, we may conclude that in considerably more than half of the patients economic and social restitution may be expected after the fourth month and will continue up to at least on an average of fifty-seven months, and that this restitution is made in the presence of residual symptoms and despite the stress and strain of the needy in a metropolitan district.

BLOOD GROUPS IN TUBERCULOSIS *

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Recently added emphasis has been given to the importance of the constitutional factor in disease through the work of Draper,[1] Kretschmer [2] and others. The work of these men has been based largely on structural or morphologic observations. It was felt that an approach to this problem from the standpoint of the basic physiologic pattern, as suggested by Draper, might also prove of interest.

With this in view, a study of the distribution of the blood grouping was made in a series of tuberculous subjects, blood type being generally regarded as an outstanding constitutional quality, and tuberculosis as representing a somatic disorder of traditionally important genotypic relationship. The only previous work appearing in the literature is that of Alexander,[3] who studied fifty cases with apparently negative results. Obviously, however, such a series is too small to warrant a valid conclusion.

The series utilized in this study was comprised of 400 cases, all but 12 of which were of the pulmonary type. The subjects were of both sexes and were racially distributed as indicated in table 1. Three hundred and fifty-two, or 88 per cent of this series, fall into the so-termed "European" group,[4] for which an apparently adequate norm has been established.

The actual typing was carried out essentially according to the simplified technic of Moss,[5] using known serums of groups II and III and the cells of the unknown subjects. The grouping of the blood specimens used for the known serums was checked by cross-agglutina-

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* From the State Psychopathic Hospital.

1. Draper, G.: Human Constitution, Philadelphia, W. B. Saunders Co., 1924.

2. Kretschmer, E.: Körperbau u. Charakter, Berlin, Springer, 1921.

3. Alexander, W.: An Inquiry Into the Distribution of the Blood Groups in Patients Suffering from "Malignant Disease," Brit. J. Exper. Path. **2**:66 (April) 1921.

4. Ottenberg, R.: A Classification of Human Races Based on Geographic Distribution of the Blood Groups, J. A. M. A. **84**:1393 (May 9) 1925.

5. Moss, W. L.: A Simplified Method for Determining the Isoagglutinin Group in the Selection of Donors for Blood Transfusion, J. A. M. A. **68**:1905 (June 23) 1917.

tion tests of both cells and serum with other blood specimens of known type, and the serums were always used fresh and undiluted. The cells to be tested were obtained by mixing a few drops of blood from a pricked finger with physiologic sodium chloride. A microscopic slide was divided into two sections by a wax pencil mark; a drop of group II serum was placed on one end and a drop of group III serum on the other. A drop of the cell suspension to be tested was added to each serum and thoroughly mixed. The slides were allowed to stand at room temperature and the cell suspension and serum were mixed frequently and examined macroscopically and microscopically for at least twenty minutes. The blood specimens were grouped according to the classification of Moss.

TABLE 1—*Racial Distribution.*

Nationality	Tuberculous Subjects	
	Number of Cases	Percentage of Total
German	81	20.25
Polish	43	10.75
Irish	41	10.25
English	38	9.50
French	15	3.75
Scandinavian	12	3.00
Scotch	11	2.75
Finnish	8	2.00
Italian	7	1.75
Negro	7	1.75
Hungarian	7	1.75
Dutch	7	1.75
Austrian	5	1.25
Hebrew	5	1.25
Mixed	92	23.00
Miscellaneous*	21	5.25

* Lithuanian, Russian, Bulgarian, Roumanian, Serbian, Swiss, Armenian, Croatian, Bohemian, Spanish, Slavic.

The results obtained have been tabulated in table 2. It will be seen from this table and from the chart that the distribution found in the total series conforms well with that of the general average of American workers [6] based on 9,600 cases. Likewise the "European" tuberculous formula seems to show no essential variation from the "European" average or normal pattern, although as compared with both average groups, the number of tuberculous subjects seems slightly low in representation in group I. Whether this observation, however, can be accorded any valid significance is highly speculative.

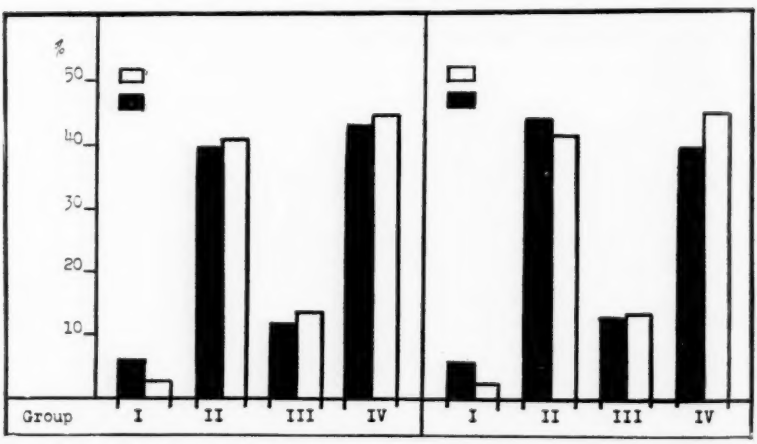
In view of the possible relation of tuberculosis to the so-called asthenic or phthisical bodily habitus, analysis was made also from this

6. Sanford, A. H.: Blood Transfusion: Indications for Its Use, Methods of Selecting Donors and a Brief Consideration of Technic, M. Clin. N. Amer. **3**:801 (Nov.) 1919. Culpepper, W. L., and Ableson, M.: Report on Five Thousand Bloods Typed Using Moss's Grouping, J. Lab. & Clin. Med. **6**:276 (Feb.) 1921.

standpoint. In this connection it should be mentioned, however, that diagnoses of habitus, although painstaking, were made impressionistically and without the application of formal anthropometric procedures; also that our total series of asthenics is admittedly rather small.

TABLE 2.—*Distribution of the Four Blood Groups in Tuberculous Persons Compared with the Distribution in Normal Persons*

Subjects	Number	Blood Groups (According to Moss) I Percentage	II Percentage	III Percentage	IV Percentage
Nontuberculous					
Average	9,600	5.8	38.7	11.3	44.2
European average	8,325	4.6	43.4	12.8	39.2
Tuberculous					
Total	400	2.3	40.2	13.5	44.0
European type	373	2.4	39.6	12.9	45.1
Asthenic (total)	120	3.4	35.8	15.8	45.0
Nonasthenic (total)	280	1.8	42.1	12.5	43.6
Productive (total)	123	2.4	37.4	17.1	43.1



Distribution of the four blood groups in tuberculous persons compared with the distribution in normal persons. The black columns on the left side of the chart represent the distribution of the blood groups in the general average of American workers; the white column, the distribution in the total series of tuberculous subjects. On the right side of the chart, the black column represents the distribution in the average European subject; the black column, the distribution in tuberculous European subjects.

However, subject to the possible limitations of these factors, no essential differences are apparent between the asthenic and the nonasthenic tuberculous groups, although it might be said perhaps that the former seems to be slightly lower in group II.

In view of the possible relation between habitus and the so-called exudative and productive types of pulmonary tuberculosis,[7] an analysis

7. Pinner, Max (Detroit Municipal Sanatorium) Personal Communication.

of the blood grouping in these types was originally planned. Unfortunately, the distribution of cases with reference to these two types was not such as to permit satisfactory comparison. It might be mentioned, however, that the series of 123 cases of the productive form does not differ noticeably from the total or asthenic formulas.

In conclusion it would seem that if this series may be regarded as satisfactory, no specific relationship can be established on the basis of the ordinary standards between blood type and tuberculosis. In corollary, from the standpoint of constitution, if there is any specific relationship between tuberculosis and genotypic physiologic pattern, this does not appear to include the quality of blood type.

It might be of some interest possibly to investigate such a series from the standpoint of Guthrie and Huck,[8] according to whom twenty-seven blood groupings are biologically possible, instead of the four ordinarily assumed.

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8. Guthrie, C. G., and Huck, J. G.: On the Existence of More than Four Isoagglutinin Groups in Human Blood, Bull. Johns Hopkins Hosp. **34**:37, 80, 128 (Feb., March, April) 1923.

THE OCCURRENCE AND SIGNIFICANCE OF ELECTROCARDIOGRAMS OF LOW VOLTAGE *

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The increasing use of the electrocardiograph in the clinical study of heart disease has brought forth many valuable graphic signs in the identification and the corroboration of myocardial disease, and also important facts bearing on prognosis.

From time to time various observers have called attention to the relationship of electrocardiograms of low voltage to disease of the myocardium (Carter,[1] Pardee and Master,[2] Lutembacher,[3] White and Burwell,[4] Clerc and Bascourret,[5] Oppenheimer and Rothschild [6]). Low voltage electrocardiograms have been recorded in patients with pericardial effusions, returning to normal after paracentesis and subsequent improvement in the patient's condition. Oppenheimer and Mann [7] also called attention to them in connection with extensive pericardial and pleuropericardial effusions. The occurrence of low voltage records in myxedema and cretinism has been described by Zondek [8] and by Thacher and White.[9]

A recent report by Sprague and White [10] was based on fifty-seven cases observed during eleven years at the Massachusetts General Hos-

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* From the Section on Cardiology, Mayo Clinic.

1. Carter, E. P.: Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborization, Arch. Int. Med. **22**:331 (Sept.) 1918.

2. Pardee, H. E. B., and Master, A. M.: Electrocardiograms and Heart Muscle Disease, J. A. M. A. **80**:98 (Jan. 13) 1923.

3. Lutembacher, R.: The Heart in Hypertension, Bull. méd. **31**:616, 1922.

4. White, P. D., and Burwell, C. S.: The Clinical Significance of Changes in the Form of the Electrocardiogram, M. Clin. N. Amer. **4**:1839, 1920-1921.

5. Clerc, A., and Bascourret, M.: Les anomalies des complexes ventriculaires electriques et leur importance pronostique dans le cours de l'insuffisance cardiaque, Rev. de med. **41**:587, 1924.

6. Oppenheimer, B. S., and Rothschild, M. A.: The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, Tr. A. Am. Phys. **39**:247, 1924.

7. Oppenheimer, B. S., and Mann, Hubert: An Electrocardiographic Sign in Pericardial Effusion, Proc. Soc. Exper. Biol. & Med. **20**:431, 1923.

8. Zondek, Hermann: Das Myxodemherz, München. med. Wchnschr. **65**: 1180, 1918.

9. Thacher, C., and White, P. D.: The Electrocardiogram in Myxedema, Am. J. M. Sc. **171**:61, 1926.

10. Sprague, H. B., and White, P. D.: The Significance of Electrocardiograms of Low Voltage, J. Clin. Investigation **3**:109, 1926.

pital. The majority (thirty-four) were of the arteriosclerotic type of heart disease; ten were classified as hypothyroidism and thirteen as miscellaneous. The total mortality in this group was 49 per cent. In eleven cases the cause of death was definitely attributed to heart disease, and in six others it was presumably due to heart disease; the cause of death in six cases was uncertain. These authors did not observe electrocardiograms of low voltage (excluding the temporary effect in hypothyroidism) in patients with normal hearts, and concluded, therefore, that such electrocardiograms are of diagnostic and prognostic importance in forming an opinion of the myocardial capacity of any person. In certain of the cases, however, there were associated electrocardiographic abnormalities, such as flutter, incomplete bundle-branch block, auricular fibrillation, complete heart block and significant T-wave negativity. These abnormalities are in themselves important and significant, and when independent of records of low voltage are indicative of myocardial disease. They are of definite prognostic importance.

MATERIAL FROM THE MAYO CLINIC

From a complete survey of all the cases in which electrocardiographic examinations were made at the Mayo Clinic from Aug. 1, 1914, to Nov. 1, 1926, it was found that 140 of them were cases in which low voltage records were unassociated with other significant graphic abnormalities, an incidence of 0.3 per cent. In our selection of cases we followed rigidly the criteria of Sprague and White, accepting those cases only in which the QRS deflections did not deviate more than 5 mm. in either direction from the base line in any of the three customary leads. The difference in electric potential was therefore not greater than 0.0005 volt. All records were standard, that is, a string deviation of 1 cm. for each millivolt of current.

All records displaying flutter, auricular fibrillation, incomplete bundle-branch block, significant T-wave negativity, complete and partial heart block, delayed auriculoventricular conduction and the ectopic tachycardias were rejected.

CARDIAC DISEASES

There were twenty-one cases of arteriosclerotic cardiac disease; sixteen patients were men and five women. The youngest was 44, the oldest 80, and the average age in the group was 64. There were two cases in which angina pectoris occurred and eight in which there was congestive heart failure.

Information has been obtained regarding fifteen patients. Five (33 per cent) have died from heart disease in an average of one and one-half years. One death was not related to the heart, and the

cause of another death was not obtained. Eight patients (53 per cent) are alive; seven report their health improved, while that of one is unchanged.

At necropsy in one case marked sclerosis of the coronary arteries was found. The heart was hypertrophied, weighing 679 Gm. This was the only case of hypertension in the group. The myocardium showed fatty changes.

Hypertensive Cardiac Disease.—There were nine cases of hypertensive cardiac disease. Six patients were men and three were women. The youngest was 51, the oldest 65 and the average age 58. Only two patients presented the syndrome of congestive failure.

Five patients have been traced. One patient died from heart disease (20 per cent), but the date of death is not known. The remaining four patients (80 per cent) report their condition as being improved.

Rheumatic Endocardial Valvular Disease.—There were six cases of chronic endocardial valvular disease. The lesions were stenotic in all, involving the mitral valve in five cases and the aortic valve in one case. Two patients were men, and four were women. The youngest patient was 19, the oldest 49, and the average age was 34. Three patients had congestive heart failure.

Data have been obtained regarding four patients. Two (50 per cent) died from heart disease in an average of three and one-half months from the time of our observation. The other two patients are improved.

Syphilitic Aortitis.—There were five cases of syphilitic aortitis. Four patients were men, and one was a woman. Their average age was 38. These patients were all up and about, and their cardiac handicap was relatively slight. None had congestive heart failure or the anginal syndrome.

Three patients have been traced. One died from pneumonia; the other two patients reported that their condition was improved.

Aneurysm of the Thoracic Arch.—There was only one case of aneurysm of the aortic arch, that of a man aged 51. The aneurysm was large, but the patient reports his condition as being unchanged.

Adherent Pericarditis.—There were two cases of adherent pericarditis, both in women, aged 43 and 54, respectively. One patient had congestive heart failure. The one patient heard from reports her condition improved.

Focal Myocarditis.—There was one case of focal myocarditis. The patient, a woman, aged 24, died from this trouble, which occurred during the course of a severe infectious polyarthritis. Necropsy revealed extensive focal myocarditis, terminal bronchopneumonia and diffuse nephritis.

DISEASES OTHER THAN CARDIAC

The remaining ninety-five cases form a miscellaneous group, and in the majority of cases no evidence of cardiac disease existed, while in those with symptoms and signs of cardiac disease the degree of damage was minimal. It is necessary to discuss this group rather fully in order to show the diversified character of the cases and the relationship of low voltage electrocardiograms in apparently normal hearts to those in which cardiac disease probably existed.

Diabetes Mellitus.—Electrocardiograms of low voltage occurred in eighteen cases of diabetes mellitus. Fourteen of the patients were men and four were women. The youngest patient was 17, the oldest 72, and the average age was 54. Only three patients presented symptoms of cardiac insufficiency, and none to the degree of congestive failure. The objective cardiac examinations of these patients showed only slight, if any, cardiac enlargement and but slight muffling of the heart tones. The remaining fifteen patients did not have cardiac complaints and did not present symptoms justifying the diagnosis of organic heart disease.

It may be argued, however, owing to the relatively high incidence of arteriosclerosis in diabetic patients that many of the patients had arteriosclerotic cardiac disease. Such an argument is presumptuous in view of the facts at hand.

Fourteen patients were traced. One death only (7 per cent) could be attributed to cardiac disease. Three patients died from diabetes. Ten patients (71 per cent) are alive, five are improved, the health of three is unchanged and two are worse.

Chronic Nephritis.—Thirteen patients, seven men and six women, had chronic nephritis, and in only two instances was hypertension associated. The youngest patient was 32, the oldest 67, and the average age was 51. There was evidence of varying degrees of cardiac insufficiency in all but one case, although in no instance was the syndrome of congestive failure noted. In no case was there well defined objective evidence of cardiac disease.

Ten patients have been traced. Only one death (10 per cent) resulted from heart disease, six patients died from nephritis and three patients (30 per cent) are living; one is improved, and two are worse.

One death from nephritis occurred nine months after the electrocardiogram was obtained. Necropsy showed glomerulonephritis, chronic nephrosis, right pleuritis, bilateral hydrothorax and ascites, and terminal pericarditis. The heart was essentially normal.

Chronic Cholecystitis with Lithiasis.—Low voltage records were obtained in five cases of chronic cholecystitis with lithiasis. Three of the patients were men, and two were women. The youngest patient

was 37, the oldest 67, and the average age was 43. None of the patients presented cardiac symptoms and examination disclosed no evidence of heart disease.

Four patients have been traced; all are alive and apparently in good health.

Portal Cirrhosis.—There were four cases in this group. All the patients were men, the youngest being 26, the oldest 61. The average age was 45. The patients all complained of dyspnea and had ascites, but the symptoms were not the result of primary cardiac disease.

Data have been obtained regarding three patients. One died from cirrhosis; two are alive and report their conditions as unchanged.

Chronic Infectious Arthritis.—Chronic infectious arthritis occurred in three cases. Two of the patients were women, and one was a man. The youngest patient was 42, the oldest, 60; the average age was 50. No cardiac symptoms were elicited in any of the cases, nor did objective examination of the hearts reveal evidence of disease. All the patients are alive.

Pernicious Anemia.—There were three cases in this group; two of the patients were men and three were women. The ages were 52, 58 and 62, respectively. All the patients have died from this disease. In one case in which necropsy was performed, the heart was found to be normal.

Exophthalmic Goiter.—Low voltage electrocardiograms resulted in only three cases of exophthalmic goiter. There were two women and one man. All the cases occurred during the fourth decade of life. Two patients had congestive heart failure. Thyroidectomy was performed eventually in all instances. Two patients have been traced. One patient died from tetany two years after operation, and the other is alive and well.

Adenomatous Goiter Without Hyperthyroidism.—Three cases occurred in this group; one of the patients was a man and two were women. The ages ranged from 38 to 52. There were no cardiac symptoms or signs of heart disease in any case. All the patients are alive and well.

Myxedema.—There were two cases of high grade myxedema. This observation, in the absence of organic heart disease, has been emphasized by White and Thacher and others. The patients were both women, aged 40 and 44, respectively. No evidence of organic heart disease existed. Both patients are alive and well and are under treatment.

Low Basal Metabolic Rate (Not Myxedema).—There was only one case in this group, that of a man, aged 47. There was no evidence of organic heart disease. No information regarding this patient is available.

Syphilis of the Central Nervous System.—There were two cases in this group; both patients were men, aged 50 and 57, respectively. No evidence of cardiac disease existed. Both patients are alive; the condition of one is improved, while that of the other is worse.

Addison's Disease.—In this group there were three cases; all the patients were men from 31 to 50 years of age. Two patients complained of shortness of breath, which was probably related to the associated asthenia, as no evidence of heart disease was demonstrable. Two patients died from Addison's disease, and the other is alive and somewhat improved on epinephrine therapy. Necropsy in one case revealed no cardiac changes.

Secondary Anemia.—Two cases of moderately severe secondary anemia were included in this series. They were both in women in the fourth decade of life. No evidence of cardiac insufficiency existed. One patient that was traced is dead, but the cause of death was not ascertained.

Cancer.—Two cases of cancer occurred in this group. Neither patient was cachectic. The stomach was the seat of cancer in one and the hepatic flexure of the colon in the other. Both were men, aged 36 and 68, respectively. There was no evidence of cardiac disease in either case. Both patients are alive, seventeen months and five years after operation.

Mediastinal Lymphosarcoma.—There was one case of mediastinal lymphosarcoma in a man, aged 36. There was no evidence of organic heart disease. Death occurred from the malignant process fifteen months after observation.

Pulmonary Emphysema.—A case of pulmonary emphysema occurred in a man, aged 58. No observations indicative of heart disease were demonstrable. No word has been received from this patient.

Postoperative Ventral Hernia.—Postoperative ventral hernia was seen in one patient, a woman, aged 61. She presented no evidence of heart disease. She is alive and well seventeen months after operation.

Chronic Nervous Exhaustion.—This group comprised thirteen cases; one patient was a man and twelve were women. The youngest patient was 27, the oldest 50, and the average age was 40. In no instance did evidence of heart disease exist. Ten patients regarding whom information has been received are alive.

Benign Prostatic Hypertrophy.—A man, aged 66, had benign prostatic hypertrophy. He presented no symptoms or objective evidence of heart disease. He was relieved by operation, and is alive and well eighteen months after the examination.

Miscellaneous Group.—In this group there were fourteen cases. These included patients in whom examination did not disclose any

pathologic condition and patients with constipation and vague abdominal complaints. There were nine men and five women; their ages ranged from 11 to 67 years. No evidence of heart disease existed in any case. The nine patients who have been traced are all living.

COMMENT

It is of interest to note that electrocardiograms of low voltage independent of significant graphic abnormalities were less frequently associated with frank cardiac disease than with other diseases. The incidence was approximately 1 : 2. Another striking observation is the fact that among the patients with primary cardiac disease nine, or 30 per cent of those traced, are known to have died from cardiac disease. This is a smaller percentage than one would anticipate in a group of this type. Among the patients with various types of diseases, only seventeen (2 per cent) showed evidence of heart disease, and of the seventy traced, only two (3 per cent) died from heart disease.

These data, we believe, indicate that electrocardiograms of low voltage unassociated with other electrocardiographic abnormalities do not deserve the emphasis accorded them by some authors, and that they occur in records of normal hearts. Their occurrence in organic heart disease apparently does not indicate unusually serious disease, and the mortality figures in this study fail to justify much prognostic importance to their occurrence. It is possible, however, that the transition of complexes of normal voltage to those of low voltage during the course of heart disease may be significant. More records showing this phenomenon are necessary before definite conclusions are justified.

SUMMARY AND CONCLUSIONS

This study comprises 140 cases presenting electrocardiograms of low voltage. This in our experience is an incidence of 0.3 per cent. All cases presenting associated abnormalities, such as auricular flutter, auricular fibrillation, incomplete bundle-branch block, significant T-wave negativity, complete heart block, partial heart block, delayed auriculoventricular conduction and the ectopic tachycardias, were excluded in this study. These associated observations in themselves are significant, and when considered in conjunction with records of low voltage, they are confusing, and obscure the true issue. The criterion for the selection of cases was a record in which the QRS deflection did not deviate more than 5 mm. in either direction from the base line in any of the three customary leads. All records were standard; that is, a string deflection of 1 cm. corresponding to 1 millivolt of current.

There were forty-five cases (32 per cent) in which cardiac disease predominated, including: (1) arteriosclerotic cardiac disease, 21 cases; (2) hypertensive cardiac disease, 9 cases; (3) rheumatic endocardial

valvular disease, 6 cases; (4) syphilitic aortitis, 5 cases; (5) aneurysm of the thoracic arch, 1 case; (6) adherent pericarditis, 2 cases, and (7) focal myocarditis, 1 case.

The large group was composed of ninety-five cases (68 per cent) of various types of disease: (1) diabetes mellitus, 18 cases; (2) chronic nephritis, 13 cases; (3) chronic cholecystitis with lithiasis, 5 cases; (4) portal cirrhosis, 4 cases; (5) chronic infectious arthritis, 3 cases; (6) pernicious anemia, 3 cases; (7) exophthalmic goiter, 3 cases; (8) adenomatous goiter without hyperthyroidism, 3 cases; (9) myxedema, 2 cases; (10) low basal metabolic rate (not myxedema), 1 case; (11) syphilis of the central nervous system, 2 cases; (12) Addison's disease, 3 cases; (13) secondary anemia, 2 cases; (14) cancer, 2 cases; (15) mediastinal lymphosarcoma, 1 case; (16) pulmonary emphysema, 1 case; (17) postoperative ventral hernia, 1 case; (18) chronic nervous exhaustion, 13 cases; (19) benign prostatic hypertrophy, 1 case, and (20) miscellaneous group of vague abdominal complaints and negative examinations, 14 cases. In this group only 17 cases (3 per cent) revealed evidence of organic heart disease.

The cardiac mortality among the group with cardiac disease was 30 per cent, whereas the cardiac mortality in the group comprised of various diseases was 2 per cent.

From the data submitted here it is not justifiable to conclude that electrocardiograms of low voltage unassociated with other graphic abnormalities indicate serious myocardial disease or are of serious prognostic importance.

PRIMARY CARCINOMA OF THE LUNGS

FURTHER STUDY, WITH PARTICULAR ATTENTION TO INCIDENCE, DIAGNOSIS AND METASTASES TO THE CENTRAL NERVOUS SYSTEM

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Primary carcinoma of the lungs has become a clinical and pathologic entity of importance only in the last two decades. The pathologist of the nineteenth century was apparently under the influence of Virchow's statement to the effect that those organs which are frequently the seat of a metastatic involvement by malignant tumors are only in rare instances the seat of a primary new growth. The lungs were usually quoted as an example. Since from the circulatory point of view these organs are the convergent point of the body, malignant cells which happened to invade the blood or lymph streams invariably reach the lungs, where they form secondary nodules or masses, the latter not infrequently overshadowing that of the primary growth. Moreover, the failure of the pathologist to demonstrate grossly a secondary involvement of the lung by tumor is at present not regarded as being conclusive proof of the actual absence of tumor in the lungs. Numerous investigators [1] have shown that with tumor elsewhere clumps of blastomatous cells (metastatic) can almost always be detected in the lungs on careful histologic investigation.

The foregoing should lead, then, to the belief that whenever, in the presence of a widespread tumor anywhere in the body, a tumor is found in the lungs, the lesion in the latter ought to be considered as metastatic.

With improved pathologic and clinical methods of investigation, however, this belief has been refuted, and recently evidence has accumulated to show that primary carcinoma of the lungs is of relatively frequent occurrence. Nevertheless, the suddenness with which it has emerged from obscurity has impressed observers. It is claimed that the tumor in these organs possesses peculiarities uncommon to epithelial malignant disease found elsewhere in the body. The most debated points at present are its incidence, the methods by which it can be diagnosed in the clinic and, finally, the occurrence of metastases. These three points will be considered separately.

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* From the Surgical and Pathological Departments of the Peter Bent Brigham Hospital and the Medical Clinic of the Massachusetts General Hospital.

1. Schmidt, M. B.: Verbreitungswege der Carcinoma, Jena, 1903. Goldmann, E. E.: Studien zur Biologie der Bösartigen Neubildungen, Beitr. z. klin. Chir. **72**:1, 1911.

I. INCIDENCE

Recent literature abounds with reports on primary carcinoma of the lungs. A startling increase in primary pulmonary cancer has been noted at necropsies, and this is said to be out of proportion to cancer in general. The published statistics include material from the largest clinics, particularly those of Germany, extending over a long period of time.

In 1920, Lubarsch [2] collected reports of 450 cases from the German literature, and found the condition in 4.5 per cent of all necropsies. Similarly, Seyfarth,[3] in 1924, reported 307 cases from the Pathologic Institute of Leipzig alone, this figure representing 8 per cent of all necropsies performed in that institute.

Of particular interest are the 246 cases reported by Kikuth,[4] whose necropsy material extended over a period of thirty-five years (from 1889 to 1923). According to Kikuth, primary carcinoma of the lungs represents 9.5 per cent of all cases of cancer in the Pathologic Institute

TABLE 1.—*The Incidence of Primary Carcinoma of the Lungs in Hamburg-Eppendorf-Krankhaus*

From 1889 to 1899,	10 primary cancers of the lungs
From 1900 to 1911,	90 primary cancers of the lungs
From 1912 to 1923,	146* primary cancers of the lungs

* The yearly number of necropsies in Hamburg doubled from 1889 to 1923.

of the Hamburg-Eppendorf Hospital. In 1923, the number of primary pulmonary cancers equalled one third of the number of carcinomas of the stomach found at necropsies in this large municipal hospital. Figure 1, taken from Kikuth, illustrates the rapid increase in the number of these primary growths in Hamburg-Eppendorf.

There is another municipal hospital in Hamburg, the Hamburg-Barmbeck, which is about as large as the Hamburg-Eppendorf, and which deals with a similar type of patient. In a recent investigation, Breckwoldt [4a] reached the conclusion that the incidence of primary pulmonary cancer in this hospital has not changed since the opening of the institution in 1913. The same author, by carefully analyzing the figures and charts as given by Kikuth, states that the increase of this disease noted in the Hamburg-Eppendorf is only apparent.

2. Lubarsch, O.: Einiger zur Sterblichkeits-und Leichenöffungs-statistik, Med. klin. **10**:299 (March 9) 1924.

3. Seyfarth: Lungenkarzinome in Leipzig, Deutsche med. Wchnschr. **50**:1497 (Oct. 31) 1924.

4. Kikuth, W.: Ueber Lungencarzinome, Virchows Arch. f. path. Anat. **255**: 107, 1925.

4a. Breckwoldt, Richard: Zur Frage der Zunahme der Lungenkrebse, Ztschr. f. Krebsforsch. **23**:122, 1926.

Though dealing with smaller figures, reports from other clinics in Europe and in this country are, however, not less expressive as to the frequency of primary pulmonary cancer. These statistics, showing an incidence of from 5 to 6 per cent of all necropsies, are particularly impressive when compared with earlier figures given by Fuchs [5] and Pässler.[6] In 12,307 necropsies performed in Breslau from 1854 to 1885, Fuchs found primary carcinoma of the lungs in only 0.065 per cent; Pässler found 0.18 per cent among 9,246 necropsies performed in Munich from 1881 to 1894.

The relative frequency of this disease as seen at present in the clinic and at necropsy, as compared with old observations, is beyond any contest. The question arises, however, whether the noted increase

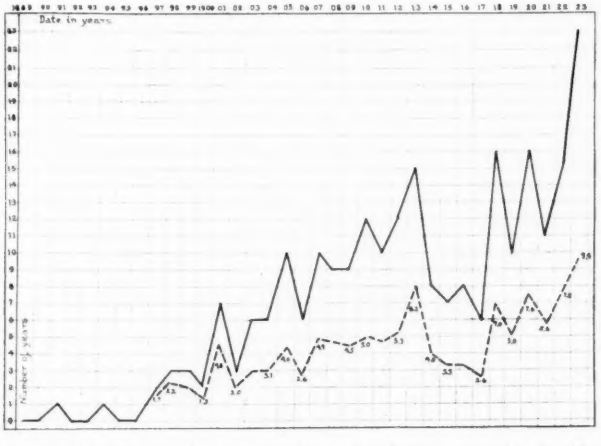

Fig. 1.—Rapid increase in the number of primary growths in Hamburg-Eppendorf (Kikuth). The solid line indicates incidence of primary carcinoma of the lungs; the broken line, the percentage relationship of primary carcinoma of the lungs to all carcinoma.

is an actual, that is, absolute, increase in the occurrence of carcinoma in general and of primary carcinoma of the lungs in particular, or whether the increase is only apparent.

The rise in the morbidity and mortality from cancer in general for the last two or three decades has been heralded by various investigators. Some observations (in this country) are to the effect that cancer is steadily increasing in frequency, the increase being a real

5. Fuchs: Beitr. z. Kenntnis des Primären Geschwülstbildungen in der Lunge, Inaug. Dissert., Munich, 1886.

6. Pässler, H.: Ueber das Primäre Carcinome der Lunge, Virchows Arch. f. path. Anat. **146**:191, 1896.

one. In a recent study, Wells[7] attributes no value to the existing cancer statistics in this country. European observers like Lubarsch (Germany), Staehelin (Switzerland) and Ménétrier (France) are either skeptical or actually opposed to the idea that the increase in the incidence in cancer noted lately is a real one. Lubarsch,[2] in his investigation on the occurrence of cancer in Germany, could draw no definite conclusions as to its increase. Hanf,[7a] in a work inspired by Lubarsch, recently investigated the incidence of primary cancer of the lungs in the Pathologic Institute of the University of Berlin. Her figures show that there was no increase in this malignant disease in this institute for the last twenty years. Staehelin,[8] referring to noted Swiss statisticians, is of the opinion that cancer is not increasing in frequency. He quotes Jessen, who investigated the cancer mortality in Basel during the period from 1870 to 1919, with a negative result as to the rise in the morbidity and mortality from cancer. Since the appearance of Staehelin's paper, investigations for other cities in Switzerland were reported by Renaut[9] and Carrière,[10] who confirmed the observations made by their predecessors.

TABLE 2.—*Incidence of Cancer in Lausanne (Renaut)*

	1901	1920		1901	1920
Cancer of the tongue	50	55	Cancer of the pancreas	48	78
Cancer of the uterus	355	321	Cancer of the lungs	15	50
Cancer of the vagina and vulva	21	18	Cancer of the ovaries	58	78
Cancer of the intestines	190	338			

In France, Ménétrier[11] affirms that cancer is as frequent now as it was a century ago. This scientist bases his opinion on a careful investigation of Parisian statistics and also on his fifty years of clinical and pathologic observations.

It is remarkable that the figures in the majority of European statistics show an increased incidence in visceral cancer and no corresponding rise in external cancer. Table 2, taken from Renaut,[9] shows the

7. Wells, G. H.: Relation of Clinical to Necropsy Diagnosis in Cancer and Value of Existing Cancer Statistics, J. A. M. A. **80**:737 (March 17) 1923; Cancer Statistics as they Appear to Pathologist, ibid **88**:399 (Feb. 5) and 476 (Feb. 12) 1927.

7a. Hanf, Dora: Zur Frage der Zunahme der Lungenkrebse in den letzten Jahren, Virchows Arch. f. path. Anat. **264**:366, 1927.

8. Staehelin, R.: Ueber die Zunahme des Primären Lungenkrebses, Klin. Wchnschr. **4**:1853 (Sept. 24) 1925.

9. Renaut, A.: Einige Belege und Betrachtungen zur Verbreitung und Statistik der Krebses, etc., Schweiz. med. Wchnschr. **56**:106 (Feb. 6) and 132 (Feb. 13) 1926.

10. Carrière, quoted by Imbert: L'augmentation du frequence du cancer est-elle reelle ou apparent? Bull. de l'assoc. franç. pour l'étude du cancer **15**:141 (April) 1926.

11. Ménétrier, M. P.: La frequence du cancer, Bull. Acad. de méd. **95**:177 (Feb. 23) 1926.

incidence in Lausanne of these two types of cancer in the years 1901 and 1920, respectively.

In England and Wales, the rate of cancer of the skin for men over 35 in 1868 was 45.7, and in 1909 it was 43.5. The rate for women over 35 years of age for cancer of the breast, uterus and ovaries was 117 in 1888; in 1909, it was 121, and in 1919, it was 127.

The foregoing may be explained plausibly on the basis that, with the improvement of modern methods of diagnosis, deep seated visceral cancer is more readily discovered now than formerly. Thus, for instance, the increase in the occurrence of prostatic carcinoma for the last twenty years is due to progress in genito-urinary surgery resulting in an increased number of removed prostates examined histologically. On the other hand, a noticeable decrease of carcinoma of the thyroid is due to early extirpation of hyperplastic glands, which in a number of instances would have become malignant.

Opinions are also to the effect that the increase in the occurrence of cancer analogous to the increase in degenerative disease in general is due to increased human longevity.

Thomas,[12] for instance, relates that for centuries before and after the time of King Tut-Ankh-Amen down to the discovery of America the average length of life was eighteen years; at the time of the French Revolution, it had increased to thirty-three years; at the time of the Civil War, it had advanced to approximately forty-five years; at present, it is about fifty-seven years. Ten of these added years, says Thomas, have been contributed during the last two decades. The importance of such facts is evident in connection with the well known "cancer age."

In a comprehensive review on the progress of medicine, the French clinician and hygienist Apert [13] also stresses the fact that the increased incidence of cancer during the last two or three decades is due partly to the lengthening of human life.

From the foregoing, it would appear that cancer in general, and primary pulmonary cancer in particular, owes its increase (1) to improved medical training and better diagnostic methods; (2) to improvement in sociologic conditions of the masses leading to their larger attendance at hospitals, and (3) to progress in hygiene and preventive medicine resulting in increased human longevity.

The increase, therefore, of all cancer, as well as that of primary carcinoma of the lungs, is in all probability more apparent than real.

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12. Thomas, B. A.: The Influence of Urology on Longevity, J. A. M. A. **86:**1957 (June 26) 1926.

13. Apert, E.: La mort recule, Rev. de deux mondes, **27:**121 (May) 1925.

II. DIAGNOSIS

The clinician of the nineteenth century was poorly armed with accessory methods for the diagnosis of pulmonary diseases. The tubercle bacillus, which is in reality the single criterion in making the diagnosis of pulmonary tuberculosis certain, was discovered in 1882. The roentgen ray as an effective aid in the diagnosis of diseases of the chest has been applied successfully in the clinic only for the last fifteen years. Bronchoscopy is of still more recent origin, and the use of iodized oil 40 per cent is as yet in its rudimentary state. Surgical exploration in obscure or doubtful cases, as practiced in the diagnosis of abdominal or pelvic organs, has not been applied to intrathoracic pathologic conditions, since the lungs have been considered from the surgical standpoint as a *noli me tangere*. For this reason, the pathology of the lungs has remained practically an unexplored field.

The diagnosis of primary carcinoma of the lungs today is based on (1) clinical data, which include the history, symptomatology, course and physical signs, and (2) laboratory methods, such as bacteriologic examination of expectorated material, roentgen-ray examination, bronchoscopy and intratracheal injection of iodized oil 40 per cent.

There has been little advance for the last twenty-five years in regard to clinical means in the diagnosis of pulmonary diseases, and the interpretation of physical signs found in these organs in pathologic conditions has remained practically unchanged since the time of Laennec. Moreover, in primary carcinoma of the lungs the signs are amazingly scant as compared with the "amount" of tissue involved and the grave character of the lesion. Again, oftentimes they are ambiguous. The cases that follow illustrate the foregoing statements.

Case 1.—In a man, aged 38, the expansion of the lungs was diminished on the left side. Vocal fremitus was diminished on the left side anteriorly and was absent posteriorly. On percussion of the left side, the note was flat from the apex to the angle of the scapula, and dull down to the lower border of the lung as far as the posterior axillary line. Anteriorly, it was dull at the apex up to the second interspace; below that, it was normal for an interspace and then was markedly tympanitic down to the base and along the axillae, as if there were air beneath the pleural cavity. On auscultation, the left side showed diminished bronchial breathing posteriorly at the apex down to the angle of the scapula. Below that, for two or three interspaces, the breath sounds were purely bronchial and close to the ear; at the base, there was distant bronchial breathing. The whispered voice corresponded. Anteriorly, the breath sounds were bronchial down to the third interspace, and below that to the base there was distant bronchial breathing.

At necropsy, a primary cancer occupying the entire apical part of the left lung was found. The rest of the lung, with the exception of the lower segments of the lower lobe, appeared as if it were split vertically in two equal parts. The anterior area was emphysematous and free of tumor; the posterior area was represented by a solid tumorous block.

Case 2.—A man, aged 64, showed on physical examination dulness over the right lower lobe with increased breath sounds, normal whispered voice and decreased tactile fremitus in this area.

At necropsy, Dr. Wolbach found a nearly complete occlusion by tumor of the right bronchus 2 cm. below the bifurcation. Anteriorly, the wall of the right bronchus was entirely replaced by new growth. The single upper lobe branch of this bronchus which could be traced was also almost entirely occluded by tumor. Below, the bronchus ended abruptly in a diffuse mass of tumor. The new growth, which had replaced the wall of the primary bronchus, extended by direct continuity over the anterior surface of the aorta, forming a layer 1 cm. thick which extended upward over the ascending position of the arch. Posteriorly, the lung was atelectatic, containing a few bronchiectatic cavities. The upper lobe was tough and fibrous, with a few nodules at the periphery.

CASE 3.—A man, aged 52, showed, on physical examination of the lungs, that the left apex was moderately dull, with a few fine râles; in the right, there was

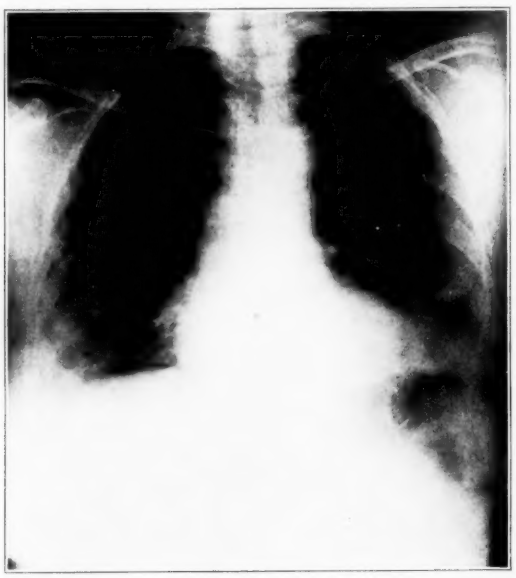

Fig. 2 (case 7).—Primary carcinoma of the lungs, showing tumor occupying the base of the left lung. The roentgenogram was taken about two months before death.

dulness and bronchial breathing from the apex to the interior angle of the scapula, with increased voice sounds. Below to the base there was flatness and a complete absence of breath sounds.

At necropsy, the right lung was found to be sclerosed and contracted, occupying only the upper half of the pleural cavity. It was diffusely infiltrated with tumor. The inferior half of the pleural cavity contained a bloody fluid. The left lung was studded with disseminated tumorous nodules, which gave to the lung on palpation a finely granular feel as if it were filled with glass beads.

As seen, the amount and character of the changes found in the pulmonary parenchyma at necropsy in the cases already mentioned are out of proportion to the signs found on physical examination. The same is true of all the cases reported in this paper which came to necropsy.

From the point of view of the symptomatology, primary carcinoma of the lungs may manifest itself in several ways. It may give symptoms referable to the organs of the chest; it is said to run a "silent" course, giving only signs characteristic of a malignant condition anywhere in the body, or again there may be only symptoms due to metastases from the primary growth.

Some reports in this country are to the effect that a correct diagnosis of primary pulmonary cancer can be made readily, provided one keeps in mind the possibility of its occurrence. Grove and Cramer [14] affirm that in a series of twenty-four cases a correct diagnosis was made by the interns of the Cook County Hospital in eight instances, or 33.3 per cent. It is of interest that in 1923 Wells [7] found in the Cook County Hospital eleven cases of primary pulmonary cancer with only one correct diagnosis. Of the thirteen patients who came to that hospital during the last two or three years (eight of whom came to necropsy), a correct diagnosis by the house officers was then made in seven instances, or in 57 per cent of the cases.

Authoritative European clinicians (de la Camp [15] and Staehelin,[8] whose opinion I share), admit great difficulties in making a correct diagnosis of primary carcinoma of the lungs. Likewise, the French clinician Rist [16] says that the diagnosis of primary cancer of the lungs is difficult. All the cases of this condition that he has observed have been diagnosed at one time as tuberculosis. In a recent article, Graham [17] affirms that "often the first symptoms of pulmonary carcinoma are those due to abscess." Indeed, there is not a single symptom or a group of symptoms which is not common to tuberculosis as well as to cancer. Loss of appetite, weight and strength, cough, expectoration, fever, etc., are common to phthisis as well as to a number of chronic respiratory infections. A diagnosis, consequently, is made only after a more or less prolonged observation of the patient with all the clinical and laboratory data at hand. In cases 4, 5 and 6, the reports of which follow, the patients' chief complaints were referred to the thoracic organs. From the standpoint of signs and symptoms, they were regarded as being more or less typical of a malignant disease of the lungs.

CASE 4.—*History of several months of cough, weakness and pain in the right side of the chest. Bronchoscopy. Diagnosis: Primary bronchogenic carcinoma of the right lung.*

14. Grove, J. S., and Cramer, S. E.: Primary Carcinoma of the Lungs, Am. J. M. Sc. **151**:250, 1926.

15. Camp, de la, O.: Zur Klinik der Primären Bronchial Karzinom, Med. Klin. **20**:1270, 1924.

16. Rist, E.: La differentiation clinique de la tuberculose pulmonaire d'avec les autres affections de voie respiratoires, Rev. de la tuberc. **4**:125, 1926.

17. Graham, E. A.: The Surgical Treatment of Pulmonary Suppuration in Children, J. A. M. A. **87**:806 (Sept. 11) 1926.

History.—A Scotch tanner, aged 62, married, was admitted to the hospital complaining of pain in the right lower quadrant of the chest and in the neck. The family history was unimportant. The past history, except for chronic alcoholism, was also negative. The present illness began several months before admission, with weakness and a cough productive of white mucoid sputum. About five months previously, he developed a steadily increasing pain in the right lower quadrant of the chest. At the same time, he became dyspneic. Four months previously, he was so weak as to be obliged to quit his work. Although his appetite had remained good, he lost 20 pounds (9 Kg.) in weight during the preceding four or five months.

Physical examination showed a poorly developed and poorly nourished man breathing with short respirations and coughing frequently with considerable distress. The right lung showed slight relative dulness posteriorly over the upper and mid-portions with dulness at the base, so that the lower border of pulmonary resonance on the right was 3 inches (8 cm.) higher than on the left. At the base, breath sounds were decreased at the upper edge of the dull area and absent below. Over the slightly dull area above, the breath sounds were slightly louder than on the left. In the right axillary region and in front there was also dulness, with decreased breath sounds. The upper level of this dulness was higher in the back than in the axilla and higher in the axilla than in front. There were no signs of displacement of the mediastinum to either side and no râles. The sputum was mucoid, blood streaked and showed no tubercle bacilli.

Roentgen-Ray Examination.—Stereoscopic roentgenograms of the chest showed an ill-defined, dense mass running posteriorly from the right hilum. The symptoms were interpreted as compatible with a primary carcinoma of the root of the right lung or possibly a localized nontuberculous inflammatory process.

Bronchoscopy.—The bronchial wall on the right just below the bifurcation was greatly thickened and was somewhat irregular, gradually narrowing down until no bronchial lumen could be seen at the point where the bronchoscope met impossible resistance. A specimen was not removed, but the appearance of the bronchial lumen suggested some malignant process infiltrating the bronchial wall in the region of the main stem of the right bronchus.

This was a typical case of primary carcinoma of the lungs: (1) the physical signs found in the chest were few and were not characteristic, (2) the cough was productive of mucoid sputum streaked with blood and was out of proportion to the signs; (3) there was pain in the chest; (4) there was considerable loss of weight in a relatively short period of time; (5) general weakness was present; (6) the roentgen rays pointed out that there was a tumor originating around the hilum of the lung, and (7) the bronchoscope showed a greatly thickened irregular bronchial wall just below the bifurcation, gradually narrowing down until no bronchial lumen could be seen.

CASE 5.—*Short history of cough and dyspnea. Intratracheal injection of iodized oil 40 per cent. Bronchoscopy with removal of tissue. Diagnosis: Primary carcinoma of right bronchus.*

History.—A Jewish cobbler, aged 51, married, entered the clinic complaining of belching of "gas" and cough. The past and family histories were unimportant. The present illness began a few weeks before admission with a cough coincident with a cold, which rapidly became persistent, severe and distressing. At the same time, the patient became dyspneic.

Examination showed a man whose respirations were labored, with a definite asthmatic stridor on expiration. He was cyanotic and orthopneic. The right pupil was smaller than the left. Examination of the chest showed flattening of

the right side of the thorax. There was dulness at the base of the right lung extending into the axilla. The breath sounds over this area were distant, and tactile fremitus diminished. The heart and trachea were displaced to the right.

The sputum was abundant, blood-streaked, and negative for tubercle bacilli. The white blood cells totalled 21,000 per cubic millimeter.

A roentgenologic investigation of the gastro-intestinal tract was negative.

Fluoroscopically, the right side of the diaphragm showed paradoxic movement. The observations indicated a partial block of the right bronchus. A reexamination of the chest, after injection of 25 cc. of iodized oil 40 per cent, showed a complete block of the bronchus of the right lower lobe and partial block of the bronchi of the middle and upper lobes. The lung on this side appeared emphysematous and distended. Most of the iodized oil had gone into the left base, where the bronchi appeared normal. The impression was that there was a block of the bronchus of the right lower lobe and a partial block of the main bronchus on the right.

Bronchoscopy.—A bit of tissue was removed and under the microscope showed a squamous epithelial cell tumor.

The patient remained in the hospital five weeks and was discharged with a diagnosis of primary bronchogenic carcinoma of the right side.

The patient in this case was slightly cyanotic and orthopneic, with a definite asthmatic stridor on expiration. His sputum had a "raspberry-jelly" like appearance, which at one time was considered characteristic of primary carcinoma of the lungs.

Of interest also are the following points: (1) The flattening of the affected side. This was due either to atelectasis of the diseased lung following obstruction of a bronchus by the tumor, or to an obliterating pleuritis as a result of the involvement of the pleura by the new growth. In primary cancer of the lung, both processes may intervene. The significance of this condition as a diagnostic criterion is, however, restricted, since it is liable to occur in numerous pleuropulmonary conditions. (2) The displacement of the heart and trachea. This also is not a feature characteristic of a pulmonary malignant condition only. Chronic cirrhotic pulmonary tuberculosis frequently furnishes the same picture. (3) Inequality of pupils due to paralysis of the sympathetic nerve involved by the new growth. Here again this sign has no value, since it is encountered in a number of organic diseases. (4) The intratracheal injection of iodized oil 40 per cent showed a complete block of the bronchus of the right lower lobe. This is, as far as I am aware, the first case on record in which iodized oil was used in the diagnosis of the primary pulmonary tumor. (5) Bronchoscopy: The removal of a bit of tissue is the most reliable criterion, and should be applied whenever possible. Unfortunately, in the majority of cases the tumor starts deep in the pulmonary parenchyma in a small bronchiole, thus making the bronchoscopic examination impracticable.

CASE 6.—*A history of cough of four months' duration associated with precordial pain. Clinical diagnosis: Primary carcinoma of the left lung. Atelectasis of the left lower lobe. Bronchoscopy. Pathologic diagnosis: Squamous epithelial carcinoma of the bronchus.*

History.—A Jewish tailor, aged 74, entered the hospital for the first time, Dec. 22, 1924, complaining of persistent cough. His family history and past history were negative, except for the fact that his father had asthma. His present illness began in September, 1924, when he developed a persistent cough productive of nonmucoid phlegm. The cough increased in intensity, and at the time of admission was almost continuous. At times it was associated with precordial pain, never radiating down the arm and with no substernal distress or discomfort. It was worse when the patient was lying down.

Physical Examination.—Dulness in the lungs was present, beginning a little below the angle of the scapula and extending to the base between the scapular line and the midback. Over the axillary region there was no definite dulness except posteriorly, where there was slight dulness at the base. Over the dull area, breath sounds, voice sounds and tactile fremitus were all decreased as compared with the right side. There was no abnormality in the quality of breath or voice sounds over the dull area. The abdomen was normal. No palpable lymph nodes were found in the neck, axillae or groins.

Roentgen-Ray Report.—A roentgenogram of the chest showed a high, fixed left side of the diaphragm. The left lung showed an irregular mass at the hilum fading out toward the periphery. The apex and right lung were clear. The impression of the roentgenologist was that there was a primary bronchogenic tumor causing atelectasis of the left lower lobe.

Bronchoscopy.—The lumen of the bronchus of the left lower lobe was greatly narrowed by thickening and hyperplasia of the bronchial wall, which at one point appeared to consist of a definite growth from the mucous membrane. A portion of this structure removed showed a new growth made up of squamous epithelial cells.

Clinical Course.—The patient suffered exclusively from pain in the chest which was relieved by morphine. His appetite was good, and the weight remained good. He died eight months after the onset of the first symptoms.

The clinical diagnosis was primary carcinoma of the lung originating in the large left bronchus.

The diagnosis of a primary bronchogenic cancer in this case, as in previous cases, was based on physical examination and observation, as well as on roentgenologic and bronchoscopic examinations.

It was noted in the foregoing that in some instances primary pulmonary cancer may run a silent course, i. e., one in which the patients' complaints are characteristic of a malignant condition anywhere in the body. The patient in case 10 in the series reported previously [18] entered the clinic with the sole complaint of progressive weakness and loss of weight of nine months' duration. These complaints dominated the clinical history during all the patient's stay at the hospital. Similar "silent" cases have been noted by Stachelin,[8] Letulle [19] and others.

Though the lack of thoracic symptoms in the course of primary pulmonary cancer has been cited by many observers, it must be pointed out that a careful study will almost always elicit signs more or less typical of bronchial irritation or of other intrathoracic disturbance. These signs are unnoticed because of the more dramatic events in the clinical history and the patients' complaints, which have overshadowed those

18. Fried, B. M.: Primary Carcinoma of the Lungs, Arch. Int. Med. **35**:1 (Jan.) 1925.

19. Letulle, M.: Le poumon, Paris, A. Maloine et Fils, éditeurs, 1924.

of the thoracic organs. The case that follows is illustrative in this respect.

CASE 7.[20]—*Five months' history of pain in the lumbar region and inability to walk. Necropsy: Primary carcinoma of left lung, with metastases to bones, brain, pleura, liver and suprarenals.*

History.—A Jewish woman, aged 57, entered the hospital, March 14, 1923, with the complaint of pain in the lumbar region extending down the left leg to the knee, and of inability to walk. The family and past history were unimportant. A tumor had been removed from the breast twenty-five years previously.

The present illness started with a dull, persistent bilateral lumbar pain five months before admission. Two weeks later, the pain extended down the left

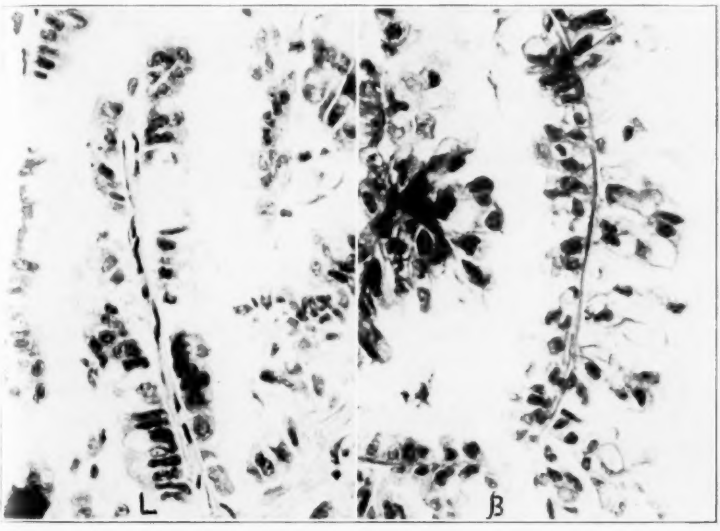

Fig. 3 (case 7).—Primary carcinoma of the lungs, showing (*L*) the histologic structure of the primary tumor in the lungs and (*B*) the metastases in the brain. The similarity should be noted.

anterior thigh. There had been trouble in walking and night sweats for from eight to twelve weeks; slight hemoptysis had occurred for two weeks.

On physical examination, the lungs were normal; the abdomen was spastic, and the left lower quadrant was definitely tender. Several small nodules were found on the left side of the cervix uteri. The blood pressure was systolic, 110; diastolic, 60. Clinically, no pathologic changes were found. Roentgen-ray examination showed an area of consolidation in the left base (fig. 3).

Following an operation for myoma of the uterus, the wound healed poorly, owing to infection. The patient coughed up blood-tinged sputum. The temperature was of a septic character. The patient died after seventy-five days in the hospital.

The necropsy revealed a primary carcinoma of the left lung occupying the left lower lobe and extending along the posterior axillary line just below the inter-

20. This case and case 8 were reported previously in detail. Cf. footnote 18.

lobar fissure. There were metastases to the pleura, bones, liver and suprarenals. In the brain a tumor nodule measuring 1.5 cm. in diameter was found in the left posterior parietal region. It was definitely adherent to the dura by clot, and its base seemed to have infiltrated the dura in places.

The pathologic diagnosis was primary carcinoma of the lungs, metastatic to the brain, bones, pleura, liver and suprarenals.

The notion that the first complaints of the patient may be, and indeed frequently are, referred to the metastatic involvement by the tumor is practically unknown. In this case particularly, the idea that the bones were the seat of a secondary new growth from somewhere in the body was not even suspected, owing, apparently, to the fact that it concerned a woman; it is still believed that the bones are usually involved by a metastatic cancer from the prostate only. It is now known that primary carcinoma of the lungs, as well as of the liver, metastasize readily to bone. Older pathologists and surgeons observed frequent involvement of the bones from mammary cancer. It is rarely seen now because the tumors of the breast are removed early. The metastasis to the brain was not heralded in this case by any signs or symptoms, or possibly it had been overlooked, due to the small size of the tumor.

The signs found on examination of the chest were indefinite, and the presence of an area of consolidation at the base of the lungs indicated a pulmonary infarct. (It will be remembered that the patient coughed up blood a few weeks before admission.)

Here, then, were unquestionable signs and symptoms referable to the organs of the chest. They were overlooked (1) because the patient's "alarming" complaints were directed to other organs, and (2) because of the lack of knowledge concerning the frequent occurrence and behavior of primary carcinoma of the lungs, particularly lack of knowledge of its power to give widespread metastases.

III. METASTASES

A. Metastases in General.—Primary carcinoma of the lungs possesses a vigorous metastatic power, and its metastases are, as a rule, widely distributed. This has been attributed to the facts that: (1) the tumor is malignant and its dissemination effected with rapidity; (2) the lungs are abundantly supplied with blood and lymph vessels, i. e., with a rich net of channels facilitating the transport of tumor cells.[21]

21. In a study of a case of primary bronchogenic cancer, Letulle and Jacquelin (Les "embolies bronchiques" cancereuses, Presse méd. **32**:825, 1924) produced evidence that the transmission of tumor from one lung to the other was effected by way of the bronchi, similar to the occasional propagation of tuberculosis from one lung to another by way of a bronchial embolus—"embolie bronchique"—as described first by the French pathologist, Sabourin. The authors have designated this method of metastases as "métastase aérienne."

It seems, however, that in malignant disease, analogous to infectious processes, the host himself has to be taken into consideration. Many years ago, Lubarsch [22] noticed that blastomatous cells which had been carried into the circulation grew there only when favored by some factors which he thought emanated from the tumor cells themselves. In his opinion, malignant cells secret a toxic substance which passes into the circulation, eliminating the factor present in normal human plasma, inhibitory to tumor cells. The fact that the tributary lymph glands in cancer show structural changes of toxic origin long before they have been involved by new growth is, in the mind of Lubarsch, the result of some kind of secretion from the tumor which prepares the terrain for its implantation. He regards the property to form metastases as a consequence of some kind of autointoxication.

To be sure, the property of a new growth to metastasize and the abundance of metastases in one or another variety of tumors depend on a number of factors, some of which will probably not be known until the final solution of the problem of a malignant condition. It would appear, however, that the rôle of the organ itself in which the tumor arises is of minor importance in the wide distribution of secondary growths. The liver, for example, gives rise to two varieties of tumors—hepatoma, or carcinoma of the liver cells, and cholangioma, or carcinoma of the bile duct.[23] Whereas metastases from the cholangioma are widespread, those from the hepatoma are surprisingly scant. In the epithelium lining the acini of the prostate, two carcinomas of different structure may arise. In one instance, the metastases are abundant; in the other, they are scant. In the lungs themselves a number of cancers do not metastasize at all, while in other cases of pulmonary cancer the regional lymph nodes only are involved by the new growth.

Observations have been made to the effect that the structure of the tumor is an important factor influencing the abundance of metastases. Soft, cellular tumors metastasize more readily than those which are poor in cells and, consequently, hard in consistency. It has also been noticed that malignant disease occurring in extreme old age shows slight predisposition to metastasize widely. Finally, paradoxic as it may appear, the abundance of carcinomatous metastases is generally in an inverse proportion to the rate of growth of the tumor; the slower the rate of growth of the neoplasm the wider are its metastases. In a study

22. Lubarsch, O.: Geschwülste. Blutveränderungen bei Carcinom. Ergebn. d. Allg. Path. **2**:566, 1895; Uber destruirendes Wachstum und Bösartigkeit der Geschwülste, Ztschr. f. Krebsforsch. **5**:114, 1907.

23. Fried, B. M.: Primary Carcinoma of the Liver, Am. J. M. Sc. **168**:24 (Aug.) 1924.

of 452 necropsies with cancer somewhere in the body, Kitain [24] found that the cancroid and scirrhus type of carcinoma furnished the highest figures of widespread metastases.

In an experimental investigation of the formation of metastases in sarcoma of the hen, Pentimalli [25] arrived at similar conclusions. This author found widespread metastases, detected macroscopically (lungs, liver, kidneys) in slowly growing tumors only. In those which grew rapidly, metastases could be disclosed only by animal inoculation of small hemorrhagic foci (red metastases) found mostly in the liver of inoculated birds. Analogous observations were made previously by Haaland [26] in experimental transplantation of sarcoma in mice.

This possibly may be accounted for by the fact that rapidly growing tumors usually kill the animal or cause the death of the patient before widespread metastases have time to develop.

Although there are no definite data concerning the approximate duration of the disease in primary carcinoma of the lungs, yet it would appear that its advance is slow. Not infrequently months of clinical observation controlled by roentgen-ray examination show a hardly perceptible advance of the growth. Very likely, then, the wide spread of metastases in primary pulmonary cancer is due also, all other conditions being equal, to its usually slow growth.

B. Metastases to the Central Nervous System.—In nineteen cases of primary carcinoma of the lungs which I have investigated, extensive metastases to the brain occurred in nine instances, in addition to wide general metastases, the occurrence of which, as said, is common in primary malignant disease of the lung. German authors have noted also that the brain is frequently involved by primary bronchogenic cancer.

Seyfarth [3] found involvement of the brain in thirty-two cases that he studied. He does not say whether the brain was examined in all necropsies in his series. Dosquet,[27] in a work inspired by Lubarsch, investigated the material of the pathologic institutes of the cities of Berlin (from 1907 to 1920) and Kiel (from 1914 to 1918). Of 105 primary cancers of the lung, 33, or 37.5 per cent, gave metastases to the brain.

The brain was examined in eleven of the nineteen cases that I have investigated. Nine of the eleven cases showed cerebral metastases.

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24. Kitain, H. L.: Zur Kenntnis der Häufigkeit und der Localization von Krebsmetastasen, etc., Virchows Arch. f. path. Anat. **238**:288, 1922.

25. Pentimalli, F.: Ueber Metastasenbildung beim Hünersarcom, Ztschr. f. Krebsforsch. **22**:64, 1924.

26. Haaland, M.: Die Metastasenbildung bei transplantierten Sarkomen der Maus, Ztschr. f. Krebsforsch. **5**:122, 1907.

27. Dosquet: Ueber die Metastasenbildung bei Primären Lungen und Bronch. Krebses, Virchows Arch. f. path. Anat. **234**:481, 1921.

This is of interest in that cancer, according to the commonly accepted theory, spreads only by way of the lymphatics, which are lacking in the central nervous system.

More recent observations, however, are to the effect that the blood stream is much more frequently invaded by cancerous cells than was commonly thought (Schmidt [28] and Goldmann [29]).

My own investigation of the pathologic material at the Harvard Medical School is in complete agreement with that of the authors quoted. Tumor cells were invariably found in the vessels (lumen or wall) of various calibers, and also in the capillaries of almost every case investigated. Figure 4 demonstrates thrombosis of a larger pulmonary vein by cells of a bronchogenic cancer. Carcinomatous cells, as seen, have invaded the vascular coats and have also ruptured the vessel wall. Again, it is of interest to note that in almost every case studied, the brain contained numerous tumor nodules, invading practically every part of the hemispheres and also the cerebellum, which affords definite evidence for hematogenous transport, with possibly "showers" of emboli carried to various structures of the brain.

C. The Cause of the Frequent Occurrence of Cerebral Metastases in Primary Pulmonary Cancer.—The strikingly frequent occurrence of metastases of the brain in primary carcinoma of the lungs, an occurrence which is relatively rare in extrapulmonary cancers, in addition to the factors mentioned, is particularly favored by the absence of any barrier between the lungs and the brain. A cell embolus from a pulmonary cancer passes, of course, from the pulmonary vein and heart directly into the cerebral circulation. A similar embolus from elsewhere in the body on its way to the central nervous system passes primarily through the "sieve" of the lungs, the latter serving as a barricade, keeping back the advance of the growth.

Cancer of the breast, as shown by Goldmann,[29] reaches the lungs with great frequency. The tumor emboli are, however, caught by the pulmonary capillaries in which they are, so to speak, immured. Moreover, they lead frequently to the formation of local infarcts followed by organization and destruction of the metastatic neoplastic cells. This has been confirmed in a recent investigation by Stern.[30]

Lubarsch affirms that both the lungs and the brain are acid containing organs, and that cells of a pulmonary cancer reaching the brain find themselves, consequently, in conditions favorable to their further development. Burrows,[31] too, believes that for metastases to localize in

28. Footnote 1 (first reference).
29. Footnote 1 (second reference).
30. Stern, A.: Das Schicksal eingeschwemmter Geschwülstzellen in der Lunge, Virchows Arch. f. path. Anat. **241**:219, 1923.
31. Burrows, M. T.: The Mechanism of Cancer Metastasis, Arch. Int. Med. **37**:454 (April) 1926.

distant organs or tissues these points of localization not only must be sites in which the circulating stimulus can collect, but also must contain an ample collection of other nutrient substances for the growth of the cells.

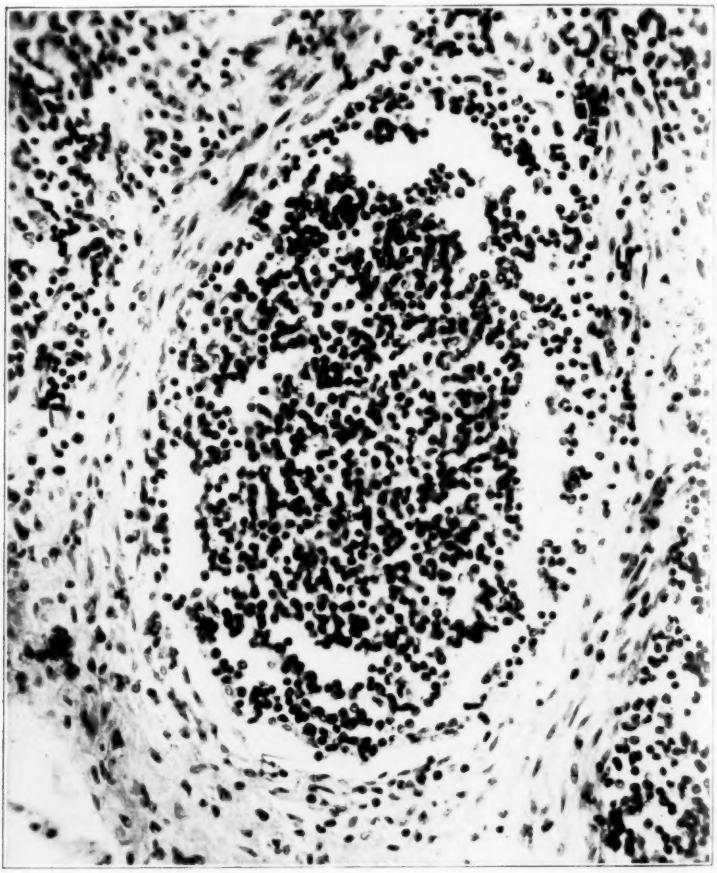

Fig. 4.—Primary carcinoma of the lungs, showing thrombosis of a pulmonary vein by tumor and tumor cells infiltrating the vascular wall which has ruptured in one area (upper part). A small celled, bronchogenic cancer.

Besides the chemical composition of the brain invoked by Lubarsch to explain the success of the metastatic growth, there is, I think, another factor: the anatomic and physiologic condition that plays the outstanding rôle and is indeed more favorable (for the growth) in the brain than in the lungs. In bronchogenic cancers, there occurs, as a rule, a more

or less extensive atelectasis of the healthy part of the involved lung, accompanied by wide necrosis of the tumor itself, interfering undoubtedly with the advance of the growth. In the brain, however, the tumor is provided with an excellent blood supply—a primordial factor indispensable for the growth of tissues in physiologic, as well as in pathologic, conditions. Moreover, Ewing [32] affirms that there is, as a rule, an increased anaplasia and more rapid growth in metastatic tumors in general.

The five case histories which follow have a twofold interest: In the first place, in all of them the complaints were referred to the cerebral metastases, and the primary pulmonary tumor either was accidentally found following an operation for removal of the metastatic tumor or was a postmortem surprise. In the second place, in the presence of such a double lesion with dominating intracranial symptoms, should a surgical attempt be made to remove the cerebral lesion? This has been recently discussed by Grant [33] from the Surgical Clinic of the Peter Bent Brigham Hospital.

CASE 8.—*An adult with acute psychosis classed as an intracranial tumor suspect. Death without operation. Necropsy: Primary carcinoma of the lungs with generalized metastases to the brain, leptomeninges, suprarenals, liver and lymph nodes.*

History.—A man, aged 55, entered the hospital, Oct. 23, 1921, complaining of severe headaches, tinnitus of the left ear, unsteadiness of gait, projectile vomiting, difficulty in talking, hallucinations and Bell's palsy. He had always been healthy up to September, 1921. The family history was negative.

The present illness began suddenly on Sept. 20, 1921, when the patient was brought home from work with a paralysis of the left side of the face. At the same time he was disoriented as to time, place and person for a few minutes. Since that time he had been restless and wandering mentally, and his speech had been thick and hard to understand. A few days later he developed projectile vomiting and hallucinations of death.

Physical examination showed an emaciated and disoriented man. The objective symptoms may be summarized as follows: 1. Restlessness and inability to cooperate. 2. Bilateral blurring of the nasal margins of the disks. 3. Protrusion of the tongue slightly to the left. 4. Blood pressure: systolic, 160; diastolic, 80. 5. Eleven cells in the spinal fluid. The fluid was positive for sugar and negative for globulin. In addition to these positive features, the blood Wassermann reaction was negative; the hemoglobin was 90 per cent, and the leukocyte count was 7,800 per cubic millimeter. The temperature was normal. Roentgen-ray examination of the head and sinuses did not show any abnormalities. The patient died after sixteen days in the hospital.

The impression was that possibly an alcoholic psychosis was present.

At necropsy, the primary tumor was found to occupy the entire lower lobe of the left lung. In the brain, metastases were found in the floor of the fourth ventricle on the right; in the lateral ventricle on the surface of the caudate nucleus; beneath the cortex and at the inferior and lateral aspect of the tip of the occipital lobe; in the center of the temporal lobe, and in the leptomeninges.

32. Ewing, J.: Neoplastic Diseases, ed. 2-d., 1922, p. 86.

33. Grant, F. C.: Concerning Intracranial Malignant Metastases, Ann. Surg. **84**:635, 1926.

The features of remarkable interest in this case were: the absence of any complaints referable to the respiratory organs; the sudden onset of the disease with cerebral symptoms and the unusually extensive metastases (brain, multiple—leptomeninges, pleura, liver, suprarenals and lymph nodes). It is obvious that the physical signs in the chest had been overlooked on account of the patient's cerebral condition.

CASE 9.—*A woman with a six months' history of headaches, regarded as a cerebral tumor suspect. Operation with removal of tumor from left occipital lobe. Recovery. Pathologic diagnosis: Carcinoma metastatic from the lungs.*

History.—A Jewish housewife, aged 46, was admitted to the hospital, April 6, 1925, complaining of headaches. She had been healthy up to about five months previously, when she began to have frontal headaches which were at first mild, but which later became severe and continuous, confining her to bed. Her

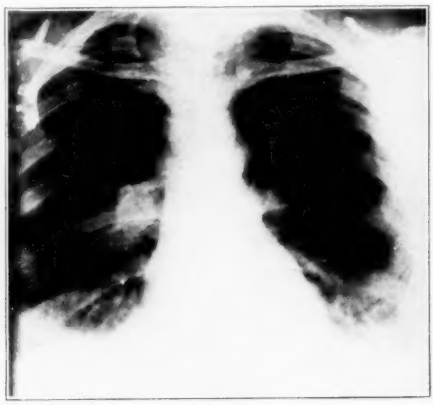

Fig. 5 (case 9).—Primary carcinoma of the lungs. A well circumscribed tumor originating in the bronchus of the right hilum.

bowels, which always had been regular, became obstinately constipated, requiring daily cathartics or enemas. Her appetite was good, but she had lost 21 pounds (9.5 Kg.) in weight since the onset of the disease.

Examination of the viscera showed nothing of importance. Clinically, no pathologic changes were present.

A neurologic examination showed slight weakness of the right side of the face, and a coarse tremor of the tongue. The reflexes were normal.

A lumbar puncture showed clear fluid which was under normal pressure. There were only lymphocytes in the fluid (45 before and 30 after hemolysis). The eyegrounds showed bilateral choked disks with hemorrhages.

The impression was that a tumor of the left side of the brain or pachymeningitis hemorrhagica was present.

The patient was operated on, and a cystic tumor as large as a hen's egg was found situated in the left occipital lobe. On histologic examination, the tumor was composed of squamous epithelial cells arranged in tubules and wide strands.

The pathologic diagnosis was metastatic carcinoma.

Roentgenologic examination showed a rounded mass in the hilum of the left lung having fairly sharp edges and being approximately 5 cm. in diameter (fig. 5).

The patient was discharged without pulmonary or cerebral symptoms five weeks after the operation (about seven weeks after admission). The diagnosis was primary carcinoma of the left bronchus with metastases to the brain.

There are analogies between this case and case 8: 1. There were no complaints referable to the organs of the chest in either. 2. In both cases the cerebral symptoms were the leit motif of the patients' complaints. It will be noted, however, that in case 8, the onset of the disease was sudden and stormy, and the cerebral lesion unlocalizable. In case 9 the onset was insidious, and the clinical picture was that of a tumor of the brain.

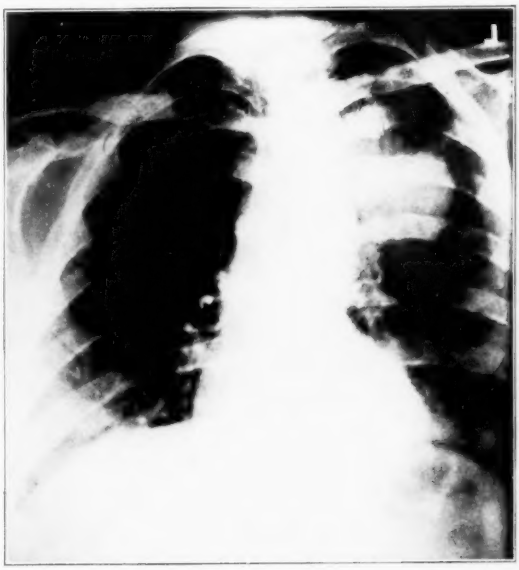

Fig. 6 (case 10).—Primary carcinoma of the lungs. Roentgenogram taken about six months after the onset of the cerebral symptoms.

CASE 10.—*A man with a four months' history of right sided paralysis, loss of speech and headache. Cerebral tumor suspect. Operation with removal of tumor from left temporal region. Pathologic diagnosis: Carcinoma, metastatic from the lungs.*

History.—An American born merchant, aged 56, whose past and family histories were negative, was admitted to the clinic, June 25, 1925, with paralysis of the right side, loss of speech and headache. He was apparently well until March 8, 1925, when he suddenly began to have attacks of twitching of the right side of the face with slight difficulty in closing his mouth, and slight difficulty in speech. Four days later, he had three such attacks, each one beginning with convulsive movements of the right side of the face, associated with disturbances in speech and paralysis of the right side of the face. His condition was progressing, and the diagnosis of tumor of the brain was made. A cerebral exploration without a subtemporal decompression was performed on March 26. No tumor

was found. He had an uneventful recovery, but his symptoms increased steadily, speech becoming much worse, his arm becoming paralyzed, and his leg becoming involved. He was given a few deep roentgen-ray treatments, with temporary relief.

The patient was well developed and well nourished. The positive symptoms can be summarized as follows: 1. The patient was in a semicomatose condition; he was incontinent and fairly responsive to strong stimulation. 2. Right-sided spastic hemiplegia with increased reflexes, bilateral ankle clonus and Babinski sign on the right were present. 3. Bilateral choked disks with hemorrhages, with formation of new tissue and exudate were also present.

The impression was that a cerebral tumor, probably in the left temporal region, was present.

The patient was operated on, June 27, 1925, and a massive, partly degenerated tumor was removed, which on histologic examination was composed of epithelial cells having a tubular arrangement. The diagnosis of a metastatic carcinoma was then made, and it was suggested that the tumor originated in the lungs.

On July 21, 1925, roentgen-ray examination of the chest showed a well circumscribed, large rounded mass in the left upper lobe anteriorly, extending from the first to the third ribs (fig. 6). The remaining lung fields were essentially normal. The impression of the roentgenologist was that a tumor of the lung was present.

On July 28, 1925, the patient had made an excellent recovery, and all his symptoms had improved considerably. He was discharged with the diagnosis of primary carcinoma of the lungs, metastatic to the brain.

This case is, to a certain extent, an intermediary between cases 8 and 9. Similar to case 8, the onset was sudden and stormy, but the cerebral lesion was difficult of localization. It was thought at first that there might be a cerebral vascular lesion of some kind. Its analogy with case 9 lay in the progressiveness, so to say, of the clinical course; this finally gave the definite picture of a tumor of the brain, which was followed by cerebral exploration.

CASE 11.—*A woman with a history of headaches accompanied by nausea and vomiting of five months' duration. Intracranial tumor suspect. Operation with removal of tumor. Death. Necropsy. Carcinoma, metastatic from lungs.*

History.—A. M. W., a trained nurse, aged 48, with a negative family history, was admitted to the hospital, Dec. 15, 1913, complaining of headaches. The past history, except for asthma of long duration, was unimportant. The onset of the present illness had been insidious. In February, 1913, she began to feel tired, although she worked without great discomfort. About September, 1913, she had an attack of severe headache, accompanied by nausea and vomiting, and required morphia for relief. Since that time similar attacks had occurred several times a week, usually being frontal, and drugs gave little relief.

Examination showed the patient to be fairly well developed and nourished, with no evidence of acute illness. The positive symptoms can be summarized as follows: Extreme degree of choked disk; protrusion of the tongue to the right, aphasia, ataxia and exaggerated deep reflexes, failing memory, poor concentration and marked depression. An examination of the visceral organs showed nothing of importance.

On Jan. 13, 1914, a tumor about the size of a hen's egg was removed from the right frontal lobe. The patient died about forty-eight hours following the operation.

Necropsy.—All parts of the brain were literally studded with tumor nodules of varying size. In the brain, more in the gray than in the white substance, were innumerable small foci, the diameters of which ranged in size from that of a

pinpoint to 2 cm.; they were filled with a clear, gelatinous substance, often coalescing. These small foci were in all sections of the brain, but in some places were much more numerous than in others. The groupings of these nodules had some resemblance to grouping of tubercles in hematogenous tuberculosis, possibly corresponding to the distribution of arterial branches.

Microscopically, the tumor was composed of columnar cells having in areas an adenomatous arrangement, and in others having a tendency to form cysts. In one section from the hippocampus, a tumor metastasis was found within the vessels. In another, a vessel was actually lined with the tumor cells with blood inside of it. Often the cells seemed to grow on the wall of the vessel itself.

From a clinical standpoint, this case closely resembles case 9 because of the insidious onset of the cerebral symptoms, by the patient's complaint, and by the positive symptoms. Additional information received from a clinic in which the patient was previously under treatment was of interest. From this report it was clear that the patient had had thoracic disturbances during three months previous to her admission to the hospital. The heart was displaced to the right, the apex beat being felt 2.5 cm. to the right from the mammillary line.

In this case also the neurologic signs and symptoms had overshadowed those of the chest.

CASE 12.—*A man, aged 41, with a six months' history of right-sided paralysis, loss of speech and severe headaches. Operation with removal of tumor. Result: Improvement. Pathologic diagnosis: Carcinoma, metastatic from the lungs.*

History.—A farmer, a native of Virginia, aged 41, with a negative past and family history, was admitted to the hospital, May 31, 1920, with paralysis of the right side of the body, inability to speak, severe headache and slight nausea and vomiting. He had had diphtheria at the age of 13, followed by slight hoarseness, and measles, mumps and chickenpox with complete recovery. He had always been well except for influenza in 1919 followed by a prolonged cough. It was thought that he had pulmonary tuberculosis, but this was not confirmed by a specialist.

The present illness began in December, 1919, when he noted weakness of the right foot and about three weeks later, weakness of the right hand. This gradually increased until the whole right side was affected. Two months later (in February, 1920) he began to have projectile vomiting. The diagnosis of a tumor of the brain was made, a subtemporal decompression performed, but no tumor was disclosed. Following operation, the patient had a flaccid paralysis of the right side including the face.

Physical examination showed a poorly developed and poorly nourished man, partially paralyzed on the right side but able to walk with assistance. He had a marked motor and sensory aphasia, flaccid paralysis of the whole right side with increased reflexes, a right facial paralysis not involving the brow, and impaired sensation of the whole right side. The diagnosis of a tumor of the brain was made again, and an operation was performed, June 9, 1920. Portions of a necrotic and infiltrating tumor were removed, which on histologic examination proved to be a carcinoma. The patient remained in the hospital twenty-eight days and was discharged improved.

On July 26, roentgen-ray examination showed the chest to be asymmetrical. The mediastinum was displaced toward the left, and there was considerable increase in the density of the shadows about the left hilum, with some clouding of the posterior mediastinum at the level of the tracheal bifurcation. The right side of the chest was distinctly larger than the left. The increased infiltration about the hilum of the lung was, according to the roentgenologist, compatible with a mediastinal tumor.

Clinically, this case was a counterpart of cases 9, 10 and 11. It is of interest in that it showed an asymmetry of the chest, the side affected being smaller. This was discussed in connection with case 5.

COMMENT

As a pathologic entity, primary carcinoma of the lungs does not possess any outstanding peculiarities not proper to carcinoma elsewhere in the body. Viewed from this angle, it therefore ought to be regarded as a part of the entire problem of malignant disease.

From a clinical standpoint, as with viscereal cancers in general, the patient ignores the early symptoms of the disease. Moreover, it is possible that in the early stages, and it is not known how long they are, the lesion runs an entirely silent course. A pulmonary tumor, when disclosed, is usually found accidentally at a routine roentgenologic examination, at necropsy, or, as in some of the cases reported, during a surgical intervention for the removal of a metastatic cerebral lesion. A clinical diagnosis of this condition, based on a few adventitious thoracic signs, found at this early stage of the disease is therefore out of the question.

As a rule, the patient consults the physician when the growth is well advanced. Here, the failure in making a prompt diagnosis is due, in the first place, to the similarities existing between this condition and a number of other chronic pulmonary diseases; in the second place, to the fact that one is actually perplexed with the "clinical irregularity" and the amazing disproportion between the physical signs and the patients' symptoms. It is still believed that symptoms and signs reflect precisely the underlying anatomopathologic lesion. This may be true in acute pulmonary conditions, but in cancer of the lung the localization of the tumor and the mode of its advance lead oftentimes to ambiguous signs confusing the most skilful clinician (cases 1, 2 and 3). At this advanced period of the disease, then, a diagnosis is based rather on the "atypical features" of the clinical picture, or it is made by exclusion. (A few valuable signs found on physical examination of the chest in a certain type of tumor have been described by Fishberg [34] in a recent report.)

In brief, it appears that there are no clinical signs which, taken alone, would make the diagnosis of a primary neoplasm of the lung certain. It is believed that the roentgen-ray examination of the chest, bronchoscopy, and the intrapulmonary injection of iodized oil 40 per cent used separately or in combination, when added to the clinical data, make the diagnosis of this disease reasonably certain.

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34. Fishberg, Maurice: Diagnosis of Pulmonary Neoplasm, Arch. Int. Med. **37**:445 (June) 1926.

CONCLUSIONS

1. European statistics are to the effect that the incidence of primary carcinoma of the lungs in relation to epithelial malignant disease in general is disproportionately high; figures given indicate that it occurs there in from 5 to 6 per cent of all post mortems. In this country, similarly, an increase in the occurrence of primary carcinoma of the lungs has been noted in the last decade.

2. Primary carcinoma of the lungs owes its statistical increase to: (*a*) better diagnostic methods and (*b*) increased human longevity. The increase, therefore, is more apparent than real.

3. A diagnosis of primary carcinoma of the lungs based on physical signs alone is never certain. Careful analysis of physical signs, combined with clinical observation and laboratory methods of investigation (roentgen rays, injection of iodized oil and bronchoscopy), makes the diagnosis of primary carcinoma of the lungs reasonably certain. Bronchoscopy, with removal of the tissue, is apparently the most reliable criterion.

4. The wide distribution of metastases in primary carcinoma of the lungs is due to: (*a*) peculiarities of its structure, i. e., it is frequently soft and abundantly cellular, and (*b*) its slow growth, since rapidly growing tumors usually cause death of the patient long before metastases have time to develop.

5. The frequent occurrence of cerebral metastases from primary pulmonary cancer, as compared with cancers from elsewhere in the body, is due to the absence of a barrier between the lungs and the brain. Metastases from elsewhere in the body on their way to the central nervous system pass primarily through the "sieve" of the lungs, in which they are usually "immured" and not infrequently perish.

6. Metastases to the brain from a primary pulmonary cancer are, as a rule, hematogenous in character.

CHANGES IN THE KIDNEY IN ANIMALS WITH INCREASED BLOOD PRESSURES WHILE ON HIGH PROTEIN DIETS*

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This paper is concerned with the changes found in the kidneys of three groups of rabbits that had been fed high protein diets for periods as long as twenty-four months. Many of the animals developed an increased blood pressure and clinical evidence of kidney injury.[1] This evidence consisted first of albumin and casts in the urine, later of an increase of the nonprotein nitrogen and urea nitrogen of the blood and finally of a decrease of carbon dioxide of the blood plasma.

The routine procedure in experiments were as follows:

Forty-eight carefully selected young rabbits were placed in individual metabolism cages. None of these animals had a spontaneous nephritis or a systolic blood pressure higher than 74 of mercury. The cages were kept out doors the year around. The blood pressures were obtained once each month by a method previously described.[2] At monthly intervals also, twenty-four hour samples of the urine were collected for p_H determinations, and single specimens were obtained by pressure over the bladder, or by catheterization, for chemical and microscopic study. Once each month enough blood was withdrawn from the marginal ear vein to determine the nonprotein nitrogen, the urea nitrogen and the carbon dioxide of the blood plasma. The methods of Folin and Wu[3] were used for the nitrogen determinations, and the method of Van Slyke and Cullen[4] for the carbon dioxide per cent by volume of the blood plasma. Monthly weight charts were kept. The special diets were given in such quantity that uneaten food was constantly present. Water was likewise provided ad libidum.

At the conclusion of the experiments the animals were killed by a blow on the neck. Sections of the various tissues were placed in 10 per cent formaldehyde and in Zenker's fluid. They were sectioned by the paraffin method, and stained with hematoxylin and eosin.

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* From the Santa Barbara Cottage Hospital.

1. Nuzum, F. R.; Osborne, Margaret, and Sansum, W. D.: The Experimental Production of Hypertension, Arch. Int. Med. **35**:492 (April) 1925.

2. Nuzum, F. R.; Seegal, Beatrice; Garland, Ruth, and Osborne, Margaret: Arteriosclerosis and Increased Blood Pressure, Experimental Production, Arch. Int. Med. **37**:733 (June) 1926.

3. Folin, O. F., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

4. Van Slyke, W. D., and Cullen, G. E.: The Bicarbonate Concentration of the Blood Plasma; Its Significance, and Its Determination as a Measure for Acidosis, J. Biol. Chem. **30**:289, 1917.

Newburg and Clarkson[5] fed high protein (26.8 to 36.2) diets to rabbits for from six to nine months. They found changes in the tubular epithelial cells of the kidneys, consisting of granulation, vacuolization, desquamation and flattening, with a resulting dilatation of the tubules. The glomeruli were not changed. Fibrosis was absent. The evidence at hand led them to believe that the kidney injury was caused either by excessive excretion of amino-acids or in part by the acid character of the urine. They did not believe that the latter factor alone was responsible.

Polvogt, McCollum and Simonds[6] gave rats diets ranging in protein content from 21 to 41.3 per cent for periods of from 250 to 400 days. These diets were "defective only in that they contained excessive amounts of protein." The kidneys were found to be large and congested, and the capillaries much distended. Hyaline material was found between the glomerular tufts and Bowman's capsule. The tubular epithelium was degenerated. In short "all the rats fed the diets high in protein had lesions of the kidneys—of considerable severity."

Newton Evans and Risley[7] gave 75 per cent casein, 58 per cent rabbit meat, 44 per cent wheat gluten and 39 per cent soy bean protein diets to four groups of rats for periods varying from seven to fifteen months. Clinical evidence of nephritis was present in the urine. Marked tubular degeneration was found in the kidneys, together with thickening of Bowman's capsule, hyaline compression of the tufts, extensive round cell infiltration and repeated instances of definite replacement of renal parenchyma by connective tissue. These investigators are the only ones to report definite evidence of connective tissue increase.

On the contrary, other investigators report negative results following high protein feeding experiments.

Drummond, Crowder and Hill[8] fed young growing rats a high protein (caseinogen) diet for 100 days. Kittens were fed a high protein (raw beef) diet for 120 days. Changes were not found in the kidneys of either species.

Anderson[9] gave a 30.5 per cent beef protein diet for "about a year" to rabbits that had been partially nephrectomized. Only hypertrophy of the remaining portion of the kidney was found.

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5. Newburgh, L. H., and Clarkson, Sarah: Renal Injury Produced in Rabbits by Diets Containing Meat, Arch. Int. Med. **32**:850 (Dec.) 1923.

6. Polvogt, L. M.; McCollum, E. V., and Simmonds, Nina: The Production of Kidney Lesions in Rats by Diets Defective Only in that They Contain Excessive Amounts of Protein, Bull. Johns Hopkins Hosp. **34**:168, 1923.

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Jackson and Riggs [10] gave a 76 per cent casein diet to five rats and a similar diet, with sodium bicarbonate added, to three rats for periods varying from ten to twenty months. They obtained only hypertrophy of the kidneys.

Osborne and Mendel [11] gave a meat residue diet (50 and 55) to growing rats for eighty days. The kidneys of these animals averaged twice the weight of normal rat kidneys, and were one-third greater in size. They did not find any changes of an inflammatory or degenerative nature.

There is a sharp contrast between the results found in these reports. In three of the four instances in which hypertrophy alone was obtained, the duration of the experiments varied from 80 to 100 days. In the instance in which other changes were found in the kidneys, the diets were continued from 250 to 450 days. The longer time interval resulted in positive results for three of the four groups of investigators here recorded.

As these reports suggest, there is increasing experimental evidence that excessive protein or other disturbances occasioned by such a diet are capable of causing degenerative changes in the kidneys.

Newburgh and Clarkson have advanced the hypothesis that certain of the amino-acids that result from protein breakdown during the processes of digestion are capable of causing increased blood pressure. It is suggested that later this may lead to degenerative changes in the kidneys. Major has demonstrated experimentally that methyl-guanidine, a product of protein metabolism in the body, is capable of producing an elevation of blood pressure. He advances the hypothesis, and likewise suggests this possible relationship to the degenerative kidney changes that follow continued hypertension.

I have attempted to obtain experimental degeneration of the kidneys by feeding high protein diets over long periods. I have been impressed with the recently advanced theory that the passage of excessively acid urines over long intervals of time might in itself be responsible for kidney degeneration. The protein in the diet has an acid ash, and produces an acid urine. The greater the amount of protein in the diet, the more acid the urine.

With this in mind, I have given diets high in protein content but containing the requisites necessary to growth and health to three groups of twelve animals each. A fourth group of twelve animals was kept as controls and fed greens, barley and alfalfa. These experiments

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10. Jackson, Henry, and Riggs, Margaret D.: The Effect of High Protein Diets on the Kidneys of Rats, J. Biol. Chem. **68**:101, 1923.

11. Osborne, T. B.; Mendel, L. B.; Park, E. A., and Winternitz, M. C.: Physiological Effects of Diets Unusually Rich in Protein or Inorganic Salts, J. Biol. Chem. **71**:317, 1927.

were continued for twenty-four months (720 days), or approximately one-half of the natural life of a rabbit. One group of animals was given a diet originally suggested by McCollum,[6] containing liver protein, 20 per cent; casein, 20 per cent; maize, 20 per cent; wheat, 30 per cent; navy beans, 5.5 per cent; cod liver oil, 2 per cent; calcium carbonate, 1.5 per cent, and salt, 1 per cent. Greens were fed at given intervals to prevent the development of deficiency diseases. The urines

Fig. 1.—Section through cortex of normal rabbit kidney to be contrasted with sections in figures 2, 3 and 4.

from these animals were acid, the p_H ranging from 5 to 6. A second group of twelve animals was given a vegetable protein (16 per cent) diet, the protein being derived from oats. In addition, cod liver oil and tomato were given ad libidum, and alfalfa was included twice a week. The urines of this group were continuously acid, the p_H averaging from 5.5 to 6. A third group was given a third type of vegetable protein (38 per cent) diet, this protein being derived from soy beans; cod liver oil, tomato and alfalfa were also given as stated previously

TABLE 1.—*Pathologic Changes in Kidneys of Animals on Liver Diet*

No. of Rabbit	Maximum Blood Pressure	Minimum Carbon Dioxide	Maximum		Urine		Duration of Experiment	Cause of Death	Kidney Changes
			Nonprotein Nitrogen	Urea Nitrogen	Reaction	Albumin			
39	108	50.0	60.0	27.3	Acid; *pH* 5.5	++ hyaline and granular casts	11 mo.	Killed	Round cell infiltration; increased cellularity of the capillary tufts; thickening of the walls of the vessels in the medullary rays; hyaline material compressing the glomeruli
42	100	48.0	50.0	27.3	Acid; *pH* 5.8	++ hyaline and granular casts	10 mo.	Broncho-pneumonia	Round cell infiltration; thickening of Bowman's capsule; diffuse areas of fibrosis; increased cellularity of the capillary tufts; thickening of the walls of the vessel in the medullary rays
44	97	50.0	47.0	30.0	Acid; *pH* 5.5	++ granular and leukocytic casts	10 mo.	Broncho-pneumonia	Tube casts; slight diffuse areas of fibrosis; increased cellularity of the capillary tufts; thickening of the walls of the vessels in the medullary rays
43	87	45.0	49.6	26.5	Acid	++ granular casts	5 mo.	Broncho-pneumonia	Round cell infiltration; tube casts
40	83	50.0	54.6	31.5	Acid	++ granular casts	4 mo.	Broncho-pneumonia	Cloudy swelling of the cells lining the convoluted tubules; round cell infiltration; increased cellularity of the capillary tufts
38	79	42.0	42.6	21.5	Acid	Trace	3 mo.	Broncho-pneumonia	Cloudy swelling of the cells lining the convoluted tubules round cell infiltration; increased cellularity of the glomeruli
45	85	51.9	42.3	21.4	Acid	—	3 mo.	Broncho-pneumonia	No change
36	95	48.1	42.3	21.9	Acid	—	3 mo.	Broncho-pneumonia	Round cell infiltration; tube casts; hyaline material compressing glomeruli
46	76	49.5	60.0	33.2	Alkaline	Trace	2 mo.	Broncho-pneumonia	Round cell infiltration; tube casts; cloudy swelling of the cells lining the convoluted tubules; adherent glomeruli

This diet gave an alkaline urine with a p_H of 9. The blood pressures in these groups became elevated in from three to four months, and continued so throughout the duration of the experiments, which in many instances were carried on for twenty-four months. There was evidence of kidney damage in each of these three groups, as shown by the presence of albumin in the urine, the frequent presence of casts and an increase of the nonprotein nitrogen and urea nitrogen of the blood. In

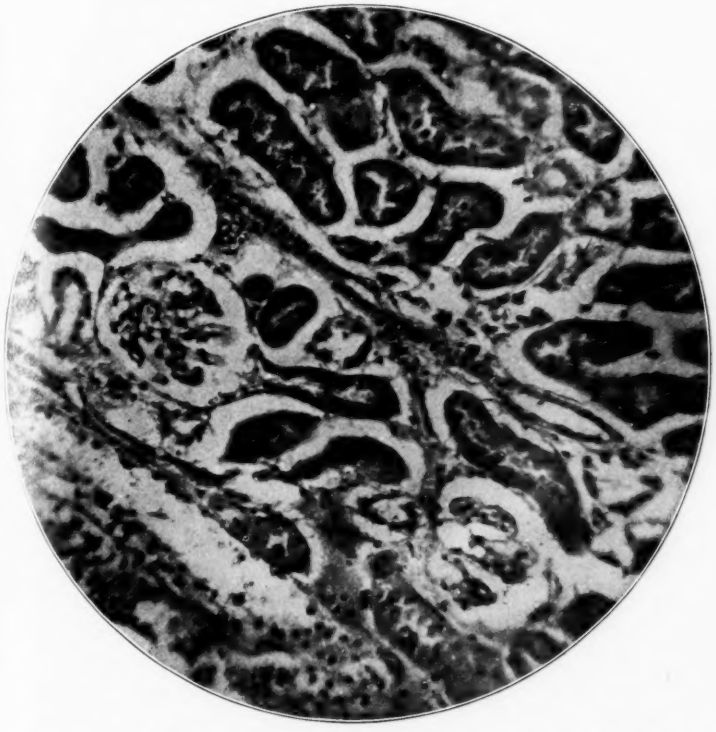

Fig. 2.—Thickening of walls of a small artery leading to two glomeruli; this thickening makes the vessel stand out distinctly in contrast to normal vessels in the kidney cortex.

many instances there was a marked reduction of carbon dioxide of the blood plasma.

A pathologic study of the kidneys of these four groups of animals was undertaken to determine what type of change had occurred, and whether these changes were more marked in the animals with excessively acid urine.

A greater degree of kidney damage, as determined by chemical studies of the urine and blood, was apparent in the animals that devel-

TABLE 2.—*Pathologic Changes in Kidneys of Animals on Grain Diet*

No. of Rabbit	Maximum Blood Pressure	Minimum Carbon Dioxide	Maximum		Urine		Duration of Experiment	Cause of Death	Kidney Changes
			Nonprotein Nitrogen	Urea Nitrogen	Reaction	Albumin			
11	100	42.0	60.0	33.0	Acid; *p*H 5.3	++ granular casts	23 mo.	Killed	Tube casts
1	90	45.0	53.1	23.1	Acid; *p*H 5.5	++ granular casts	23 mo.	Killed	Round cell infiltration; dilatation of tubules; increased number of epithelial cells in the glomeruli
3	95	47.0	57.0	38.0	Acid	+ hyaline and granular casts	23 mo.	Killed	Round cell infiltration; diffuse dilatation of the tubules
5	94	45.0	53.0	32.9	Acid; *p*H 5.9	+ hyaline and granular casts	23 mo.	Killed	Tube casts
8	98	48.0	64.0	40.0	Acid; *p*H 5.4	++ hyaline and granular casts	23 mo.	Killed	Hyaline material compressing tufts; thickening of the vessels in the medullary ray
6	97	43.0	54.1	28.0	Acid; *p*H 6.2	+	22 mo.	Killed	Round cell infiltration; scattered areas of fibrosis; diffuse dilatation of tubules; increased cellularity of the glomeruli; thickening of the walls of the vessels in the medullary rays
2	90	45.0	48.0	25.0	Acid; *p*H 6.4	+ granular casts	22 mo.	Killed	Diffuse dilatation of the tubules; increased cellularity of the glomeruli
10	88	44.0	46.2	25.0	Acid	+ hyaline and granular casts	13 mo.	Broncho-pneumonia	Round cell infiltration; diffuse dilatation of the tubules; thickening of the vessels in the medullary rays; tube casts
7	90	48.0	46.0	20.0	Acid	Trace; granular casts	13 mo.	Broncho-pneumonia	Round cell infiltration; thickening of Bowman's capsule and of the walls of the vessels in the medullary rays
4	100	53.8	60.0	39.0	Acid	++	7 mo.	Broncho-pneumonia	No change
12	90	51.0	58.8	35.7	Acid	Trace; granular casts	7 mo.	Broncho-pneumonia	Diffuse dilatation of the tubules; increased cellularity of the glomeruli; thickening of the vessel walls in the medullary rays
9	80	48.8	56.0	28.0	Acid	—	5 mo.	Broncho-pneumonia	No change

oped a more marked increase in blood pressure. A considerable degree of arteriosclerosis was also present in the aorta and in the coronary arteries of many of these animals. These changes were found in the kidneys of the rabbits on the liver diet. This diet gave the most acid urines. Five of nine animals that were on this diet for four months or longer presented diffuse dilatation of the tubules. This dilatation was due in part to a flattening of the cells lining the first and second

Fig. 3.—Compression of glomerular tuft with hyaline exudate; atrophy of cells lining convoluted tubules with dilatation of tubules; thickening of glomerular tuft.

portions of the convoluted tubules. Scattered areas of round celled infiltration were present in all these instances. Numerous tube casts were found. Six of the animals presented a marked increase in the cellularity of the capillary tufts in the glomeruli. In addition, five of these six presented a thickening of the walls of the vessels in the medullary rays. Six of the animals presented further diffuse areas of sclerosis scattered throughout the cortex. This sclerosis consisted of a thickening of Bowman's capsule and of a definite increase of fibrous connective tissue cells between the convoluted tubules.

TABLE 3.—*Pathologic Changes in Kidneys of Animals on Grain Diet*

No. of Rabbit	Maximum Blood Pressure	Minimum Carbon Dioxide	Maximum		Urine		Duration of Experiment	Cause of Death	Kidney Changes
			Nonprotein Nitrogen	Urea Nitrogen	Reaction	Albumin			
13	90	57.0	70.0	42.9	Alkaline; *pa* 7.3	+ + granular casts	22 mo.	Broncho-pneumonia	Cloudy swelling of the cells of convoluted tubules
16	84	66.0	75.0	42.9	Alkaline; *pa* 8.4	+ + granular and hyaline casts	21 mo.	Broncho-pneumonia	Tube casts; diffuse dilatation of the tubules; marked increase in the cellularity of the glomeruli
18	90	67.0	60.0	42.0	Alkaline; *pa* 8.8	+ +	21 mo.	Killed	No change
27	90	67.0	65.0	46.0	Alkaline	+ +	20 mo.	Ulcerative enteritis	Round cell infiltration; atrophy and dilatation of the tubules; thickening of the walls of the capillary tufts; diffuse areas of fibrosis
17	90	63.0	90.0	60.0	Alkaline	+ granular and hyaline casts	17 mo.	Broncho-pneumonia	Round cell infiltration; atrophy and dilatation of the tubules; diffuse areas of fibrosis
26	90	59.8	65.9	50.0	Alkaline	—	16 mo.	Infection from bite wound sustained 1 months before death	Round cell infiltration; tube casts; atrophy and dilatation of the tubules; scattered areas of fibrosis; thickening of Bowman's capsule and of the vessels of the glomerular tufts
25	89	58.6	60.0	34.0	Alkaline	Trace	13 mo.	Broncho-pneumonia	Round cell infiltration; increased cellularity of the glomerular tufts
15	83	51.9	57.7	33.0	Alkaline	—	10 mo.	Killed	Round cell infiltration; increased cellularity of the glomerular tufts; thickening of Bowman's capsule; diffuse dilatation of the tubules
28	87	57.0	49.5	25.0	Alkaline	Trace	9 mo.	Broncho-pneumonia	Cloudy swelling of the cells lining the convoluted tubules; diffuse dilatation of the tubules; thickening of Bowman's capsule; increased connective tissue in the medullary rays
14	70	45.0	52.2	28.9	Neutral	+ + granular and hyaline casts	8 mo.	Broncho-pneumonia	Cloudy swelling of the cells lining the convoluted tubules; diffuse dilatation of the tubules; round cell infiltration; increased cellularity of the tufts; thickening of Bowman's capsule

The group on the grain diet, in which the urines were also acid, although as a rule less so, exhibited changes of a similar character, but they were not so marked. In this group, round cell infiltration was present in five of twelve instances. Tube casts were occasionally found. Diffuse dilatation of the tubules was present in six of twelve instances. Thickening of the vessel walls in the medullary rays was found five times. An increased cellularity of the glomerular tufts was observed

Fig. 4.—Further marked compression of glomerulus with hyaline material and changes as recorded in figure 3.

in four instances. In one instance the tuft was compressed by hyalin exudate within Bowman's capsule. The kidneys of three of the twelve animals did not present any change.

In the soy bean group the urines were excessively alkaline, the p_H averaging 9. Two of ten animals on this diet for four months or longer presented kidneys in which changes were not found. Diffuse dilatation of the convoluted tubules and scattered areas of round celled infiltration were present in eight instances. Increased cellularity of the

glomerular tufts was noted six times. Distinct thickening of Bowman's capsule was present in three instances.

In the group of control animals, abnormal changes were not noted in seven of twelve instances. Three animals presented a few scattered areas of round cell infiltration in the cortex. Cloudy swelling of the cells lining the convoluted tubules was present once. Focal atrophy of the tubules was present once. A localized area of fibrosis of the cortex has been reported in widely varying percentages in the kidneys of rabbits which were being studied histologically for the presence of spontaneous nephritis.

COMMENT

The characteristic changes in the kidneys of rabbits fed for many months on diets high in protein were found to consist of dilatation of the convoluted tubules, flattening and vacuolization of the cells lining these tubules, scattered areas of round cell infiltration, a marked increase in the cellularity of the capillary tufts of the glomeruli, a thickening of the walls of the vessels in the medullary rays and a thickening of Bowman's capsule. Before the animals were killed and the organs obtained for study, the urine had repeatedly shown the presence of albumin and casts. The blood had shown an increase in nonprotein nitrogen and urea nitrogen, and the blood pressures were increased.

The type of tubular dilatation and the changes in the cells lining the tubules, as described, had also been carefully described by Newburgh and Clarkson [5] and is considered by them a result of high protein diets. They did not, however, find evidence of glomerular injury or of any increase of connective tissues. I found evidence of thickening of the walls of the vessels in the medullary rays and of the capillary tufts of many of the glomeruli. The thickening consisted of a definite increase of cells within the delicate walls of these vessels. The number of nuclei within the glomerular tufts was increased. The change was widely scattered throughout the kidney and did not involve localized areas. There was also an increase of fibrous connective tissue between the tubules. This increase was not like the focal scars found scattered through the cortex of kidneys which are otherwise normal. It was widespread and was found only in those instances that presented atrophy and dilatation of the tubules. These kidneys were slightly smaller than the kidneys of the control group. The average weight of the kidneys from the liver fed group was 21.2 Gm. as compared with 22.7 Gm. in the control group.

The reason for the presence of blood vessel change in the kidneys of the animals may be the fact that my experiments extended over a period of twenty-four months, whereas Newburgh and Clarkson's [5] animals were kept on high protein diets for from six to nine months.

The changes in the terminal vessels of the kidney are interpreted as a sclerosis. Sclerosis, histologically resembling human sclerosis, was found extensively in the aorta and the coronary arteries and their terminal capillaries in these groups of animals on high protein diets.[2] Such sclerosis was not found in the control group. I believe that the changes in the blood vessels of the kidneys are the same as those described in the aorta and coronary arteries, and that they represent a true blood vessel disease. The animals that presented these changes had increased blood pressures.

The factors in a high protein diet that might be responsible for the increased blood pressure that resulted in these groups, for the intimal sclerosis that was found and for the kidney changes noted are matters on which there is much discussion. Newburgh and Clarkson [5] grant that kidney change such as they describe may be due to infection acting on a kidney made susceptible to infection by the diet. They are more inclined to the belief that "the injury caused by the diet is either solely attributable to the excessive excretion of some amino acids or in part to the amino acids, and in part to the acid character of the urine." But the acidity of the urine, they feel, is by itself incapable of causing all of the injury attributable to the diet.

I have been particularly concerned with the responsibility of the passage of excessively acid urines over a long period as an aid in the production of the kidney changes I have described. The urines of the control groups of animals had a p_H of 8. The urines of the group on liver protein were the most acid of any of the groups, the p_H ranging between 5 and 6. This group presented the most marked kidney change. The group on a 16 per cent oat protein diet likewise passed acid urines, the p_H varying from 5.6 to 6. The kidney changes were somewhat less marked in this group. The urines of the group on the soy bean protein diet were excessively alkaline, and the p_H averaged 9, which is high even for a rabbit. The kidney changes in this group were less marked than those in the others. Seven of ten of these animals presented atrophy of the cells lining the tubules, with resulting dilatation. Diffuse areas of fibrosis were found in three instances. Areas of round cell infiltration were found in six. Newburgh and Clarkson found tubular degeneration of this type in animals fed on a similar diet. They concluded that some factor or factors concerned with the protein in this diet must have been responsible for the change. Martin Fischer [12] has demonstrated that excessive alkalinity, as well as acidity, is capable of producing kidney injury. The p_H of the urine of this group of animals averaged 9. It is possible that the excessive alkalinity in this group of experiments might have been responsible for these changes.

12. Fischer, M. H.: Edema and Nephritis, J. Indiana M. A. **18**:247, 1925.

SUMMARY

Kidney changes of a definite type were found in three groups of animals fed on high protein diets for a period of twenty-four months.

These changes were not found in a group of animals kept under similar conditions but fed a mixed diet of alfalfa and greens.

The urines from the groups fed the liver and oat diets were acid. Albumin and casts were found repeatedly. The nonprotein nitrogen and urea nitrogen of the blood were increased. The carbon dioxide of the blood plasma was decreased. The systolic blood pressures were increased. The urines from the group kept on a soy bean diet were excessively alkaline. Clinical evidences of kidney injury were likewise present.

CONCLUSION

It is possible that the changes described were due in part to the excessive acidity or alkalinity of the urines passed by these animals for a period approximating one half of their natural lives (twenty-four months).

YELLOW ATROPHY OF THE LIVER

ACUTE, SUBACUTE AND HEALED*

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Acute yellow atrophy of the liver is a relatively rare malady in its clinically recognizable form, and when it is of a sufficient degree of severity to exhibit its classic clinical picture, it is almost invariably fatal. There are reasons for believing, however, that this disease of obscure etiology may exist in forms which are not of such rarity or fatality as are usually ascribed to it.

For many years pathologists have described cases in which the lesions of the liver indicated a healing or healed stage of acute yellow atrophy, pointing to the probability, if not proving to the satisfaction of all, that recovery from a severe attack of the disease may occur. In 1895, Marchand [1] clearly recognized the hyperplastic, regenerative nature of large nodules of hepatic cells which are commonly found in such livers, and which in some instances seem sufficient to carry on the function of the organ. In 1909, McDonald and Milne [2] described healing stages of the disease, and in 1911, Mallory [3] classified as a distinctive group a "toxic cirrhosis" of the liver consisting of healed lesions of acute yellow atrophy which he was able to recognize by their characteristic histologic changes.

During the years immediately following the World War a remarkable increase in the incidence of acute yellow atrophy was observed in Germany. In 1913, Umber's [4] statistics showed no instance of liver atrophy among 84 cases of hepatic disease; in 1920, there were 2 cases of atrophy among 200 similar cases, and in 1921, there were 11 instances of this disease among 149 cases. Seyfarth [5] noticed a similar increase at Leipzig. Before 1915, he observed at necropsy 1 case a year on the average, while from 1915 to 1921 he saw 29 cases. Reports from pathologists and clinicians throughout Germany attested to the general increase in the disease.

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1. Marchand, F.: Beitr. z. Path. Anat. u. z. allg. Pathol. **17**:206, 1895.
2. McDonald, S., and Milne, L. S.: J. Path. & Bact. **13**:161, 1909.
3. Mallory, F. B.: Bull. Johns Hopkins Hosp. **22**:69, 1911.
4. Umber, F.: Klin. Wchnschr. 1922, **1**:1585, 1922.
5. Seyfarth, C.: Deutsche med. Wchnschr. **47**:1222, 1921.

With this increased incidence, an opportunity was afforded to study cases with reference to the possibility of atypical or milder attacks which might be followed by recovery. As a result, several cases of undoubted instances of spontaneous recovery are now on record. Such cases have been recorded by Umber,[6] Huber and Kausch,[7] Brütt [8] and others; according to Strumpell,[9] Seyfarth and Brütt, one must now recognize subacute and chronic forms of yellow atrophy.

Recently Pratt and Stengel [10] reported several cases of healed yellow atrophy or "toxic cirrhosis" from their own material and from that of Dr. Mallory's laboratory. They conclude that classic acute yellow atrophy of the liver is simply a severe, rapidly fatal type of a disease, which occurs also in a mild form; it produces few, if any, symptoms during the acute stage, but ends in cirrhosis. The authors emphasize particularly the histologic characteristics of this type of cirrhosis, described by Dr. Mallory as "toxic cirrhosis," which is readily recognizable in its healed state and distinguishable from alcoholic and other types of cirrhosis.

In a series of 130 autopsies performed in the department of pathology at the Vanderbilt medical school during the period of one year (1926), there were 3 cases of yellow atrophy, 1 acute, 1 subacute and 1 healed. These cases seemed worthy of record because of the relatively high incidence of the disease in a short series and because of the possible relation of syphilis as an etiologic factor in two cases; they are reported also in order to emphasize the possibility of recovery from a relatively severe destruction of the liver apparently without symptoms and to describe the histologic characteristics which make it possible to diagnose a healed case of yellow atrophy grossly and microscopically.

CASE 1.—*History.*—A colored boy, aged 8, entered the hospital complaining of headaches, inability to walk and blindness. The present illness began about ten months previously with headaches, which had become progressively worse. Four months before admission, his father had noticed that the boy walked on his toes and had a tendency to fall forward. The patient went to bed six weeks prior to his admission and had not been able to get up since that time. He did not have focal symptoms or fever, but he was extremely weak. The headache was worse when the patient sat up. He vomited, but the vomiting was not projectile. Up to the time of the present illness the patient had always been in good health. He did not have a history of syphilis, and the Wassermann reaction was negative. He had lost his vision, and optic atrophy and increased intracranial pressure were present.

Physical Examination.—Examination gave evidence of cerebellar tumor, and decompression was performed. Cellulitis of the neck developed, with fever and

6. Umber, F.: Deutsche med. Wchnschr. **45**:537, 1919.
7. Huber, O., and Kausch, W.: Berl. klin. Wchnschr. **57**:81, 1920.
8. Brütt, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:29, 1923.
9. Strumpell, Deutsche med. Wchnschr. **47**:1219, 1921.
10. Pratt, J. H., and Stengel, A.: Tr. A. Am. Phys. **41**:100, 1926.

rapid pulse. The condition grew worse, and the patient died fourteen days after admission.

Morbid Anatomy.—The condition was diagnosed as acute yellow atrophy of the liver, necrosis of the cerebellum (postoperative) and acute infectious encephalitis. The liver weighed 610 Gm; it appeared small. Over the convex surface were a few slightly elevated lobules from 3 to 4 cm. in diameter; these lobules were brownish; elsewhere the liver was reddish. On section, the appearance was mottled.

The microscopic appearance was that of typical acute yellow atrophy. Apparently the necrosis was recent. The skeletons of the lobules remained, the sinuses being distended with red blood cells. The liver cells next to the necrotic areas

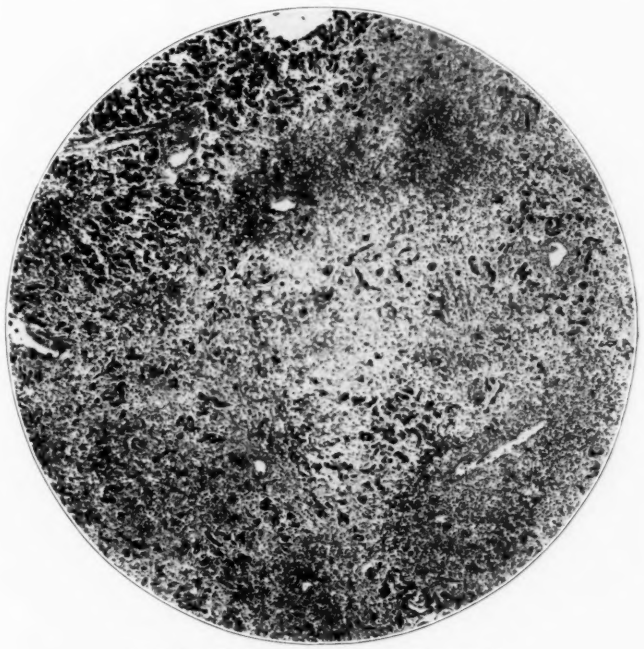

Fig. 1.—Section of the liver from case 1.

were in various stages of degeneration and necrosis. Fat vacuolization was especially prominent. Bile pigmentation was not observable and there was no regeneration. The destruction was more marked in the central portion of the lobules about the hepatic venules than around the portal areas. The distribution of the injury was, however, not uniform. All liver cells in many lobules were destroyed over extensive areas, and in others the central portion of the lobules was more or less extensively injured with advanced degeneration of all the cells in the remaining portions; adjoining such areas were large blocks of lobules in which all the hepatic cells seemed to be normal. The degeneration and necrosis seemed to advance to the lobules contiguous to those already destroyed.

In this case all the symptoms were attributed to a tumor of the brain, and the lesions indicated that the injury to the liver had occurred recently. Jaundice was not observed, and in microscopic sections there

was no evidence of a biliary obstruction. Most pathologists attribute the jaundice which occurs uniformly in severe cases of several days' duration to an obstruction in the smaller bile ducts due to plugs in their lumina. Such plugs were obvious in case 2, but were absent in this case.

CASE 2.—*History.*—A colored woman, aged 26, entered the hospital complaining of weakness, nausea and headaches. The onset of her present illness was three weeks before admission. Weakness was increasing, and she vomited four or five times a day. Two weeks previous to admission, she had given up her work

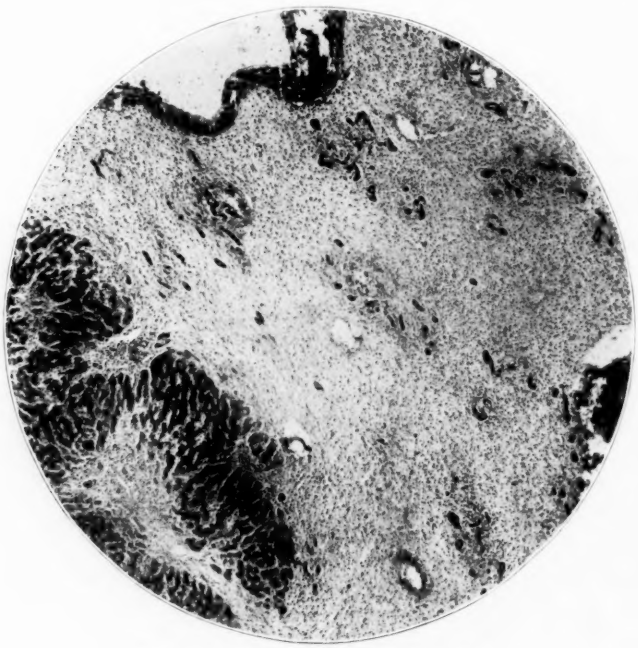

Fig. 2.—Section of the liver from case 2.

and had gone to bed. At that time she had noticed that her eyes were becoming yellow, and they had remained so. She had had three attacks of vertigo, during which she had been completely blind. Until her present illness her health had been good. She had had typhoid fever in early life and influenza and pneumonia in 1920. She was a widow and had had one child, stillborn, and a miscarriage.

Physical Examination.—Examination revealed jaundice; she did not have fever. Examination of the blood revealed: White blood cells, 6,850; red blood cells, 4,200,000; hemoglobin, 85 per cent, and clotting time three minutes. Bile, albumin and red blood cells were found in the urine. The Wassermann reaction was positive. Eight days after admission, the patient had edema of the legs and some ascites. The face was puffy. There was tenderness in the right side of the abdomen; the liver was not definitely felt. A mass was felt in the epigastrium.

The stools were clay colored. Three weeks after admission, the patient went into coma. Because of tenderness and the mass in the epigastrium, she was transferred to the surgical department. An exploratory laparotomy was performed. The gallbladder was not enlarged. The patient's condition grew worse, and she died twenty-two days after admission.

Morbid Anatomy.—Subacute yellow atrophy of the liver, and acute hemorrhagic bronchopneumonia were diagnosed. The liver weighed 570 Gm. The consistency was rather soft, and the organ was flexible. The surface was coarsely and irregularly nodular, the nodules being orange-brown and slightly elevated. The tissue between these structures was dark reddish brown, soft and fibrous. The nodular masses contained much bile pigment and were apparently areas of remaining liver tissue. The soft reddish areas were regions in which the liver cells had been destroyed.

Microscopically, there was typical yellow atrophy with a progression of acute necrosis, phagocytosis and a polymorphonuclear and large mononuclear cell exudate. Evidence of regeneration of the hepatic cells was seen, and much intracellular and extracellular bile pigment. Obstruction to the larger bile passages was not evident, although numerous bile-stained plugs were found in the smaller ones.

This case is of particular interest in that, while it is pathologically a typical instance of subacute yellow atrophy, having lasted five weeks, it serves to emphasize the difficulty of distinguishing this disease in its early stages clinically from catarrhal jaundice. It could not be determined during life that the liver had diminished in size. At the time of operation, the margin of the liver was down to the costal margin. Leucine or tyrosine crystals were not found, and the stools were described as completely acoholic.

The history of a stillbirth, a miscarriage and a positive Wassermann reaction suggests the possibility of syphilis as an etiologic factor. The number of cases of acute yellow atrophy associated with syphilis is relatively so high that many concede that in certain cases it may play an important rôle (Herxheimer, Strumpcke and Strauss). The association of acute yellow atrophy with syphilis cannot be explained as a result of hepatic injury due to arsenical therapy. A similar association was frequent in cases in which the patient was not so treated, as in the present instance in which intravenous therapy had not been used. It is doubtful that arsphenamine alone would ever produce an acute yellow atrophy in a normal person. Syphilitic infection is perhaps rather to be regarded as one predisposing condition to acute yellow atrophy, which may be precipitated by intravenous injection of arsenicals or by other causes.

Case 3.—*History.*—A white man, aged 26, entered the hospital complaining of difficult and painful urination. He had had typhoid fever and pneumonia at the age of 14. Gonorrhea had been present several years before his admission to the hospital. The present illness began about six months previously.

Physical Examination.—Examination showed: ulcer of the glans, stricture of the urethra, extravasation of urine, saddle nose, a positive Wassermann reaction and a nodular liver. The patient developed bronchopneumonia, acidosis and acute renal insufficiency, and died on the second day after admission.

Morbid Anatomy.—The condition was diagnosed as healed atrophy of the liver, acute urethritis, prostatitis, cystitis, and acute bronchopneumonia.

The liver weighed 1,150 Gm. It was tremendously distorted and lobulated, the lobules being irregular and nodular instead of smooth. The consistency was firm. Between the larger lobules were areas in which the parenchyma of the liver appeared to be missing, and in which only connective tissue, bile ducts and blood vessels remained. On section, the lobulated foci consisted of large masses of regenerated liver tissue, while the intermediate softer areas apparently did not contain parenchyma. The whole process seemed to be an old one, not active. There were fibrous adhesions over the dome. Ascites was not present.

Microscopically, in the contracted areas the cells of the liver had completely disappeared, leaving a collapsed, contracted, dense connective tissue stroma containing bile ducts which outlined the skeletons of previous lobules. Throughout this fibrous tissue there were many lymphocytes and plasma cells, and occasionally polymorphonuclear and mononuclear leukocytes. The large areas of hepatic

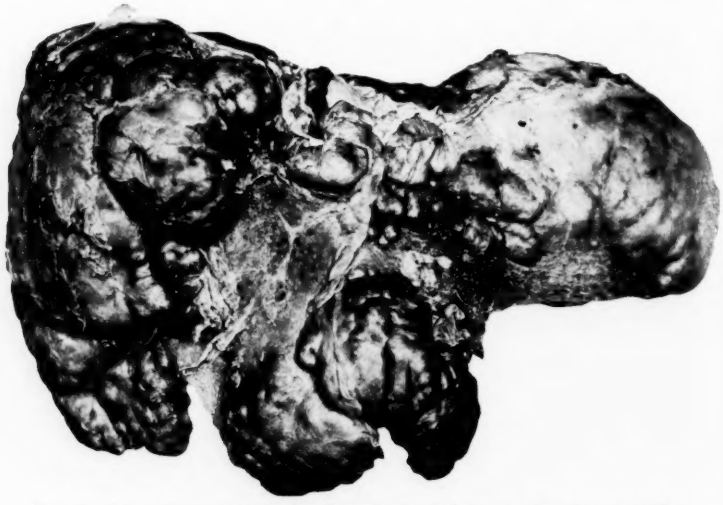

Fig. 3.—Liver from case 3, showing the healed stage of yellow atrophy.

parenchyma presented normal appearing liver cells without definite lobulation. There were areas of regenerated liver cells; these were definitely circumscribed by the dense atrophic stroma and did not show any evidence of progressive injury. The process appeared to be a completely healed stage of yellow atrophy.

The gross appearance of the liver in this case left no doubt that there had been an extensive destruction of the hepatic parenchyma, involving large areas of the liver, and that the remaining islands of liver cells had regenerated to form the massive nodules of functional tissue. There was no scarring such as one finds in the syphilitic liver as a result of the healing of gummas. The atrophic portions were not formed of scar tissue, but had the appearance of a collapsed stroma which had become indurated; this was confirmed by histologic study. The more or less regular architecture of a previous lobulation remained in the

atrophic areas. The persistence of such a lobulation, which indicates that there had been an acute destruction of all the liver cells in areas involving many entire lobules, is the histologic criterion by which Mallory was enabled to classify certain cirrhotic livers into a group which he calls "toxic cirrhosis," and which he regards as the healed stage of a destructive lesion identical in its beginning with acute yellow atrophy.

In case 3 the liver did not bear any similarity to the chronic progressive type of cirrhosis, but in its gross and microscopic features it

Fig. 4.—Section through an atrophic area in the liver from case 3. Persistence of lobulation is evident.

resembled most of the hitherto described instances of subacute or chronic stages of yellow atrophy in that there were both the extensive areas of atrophy and the large nodules of hyperplasia. In this case, however, the lesion was healed.

COMMENT

These three cases illustrate the series of events that may result from an acute yellow atrophy, namely, the acute, subacute and the healed stages. Intermediate stages between the subacute and the healed have been recorded; these deserve to be called chronic. Such are the cases

studied by Marchand (6 months), McDonald and Milne (7 months), and others. In case 2, necrosis was still advancing after the patient had been ill with jaundice for more than four weeks. Though the clinical history referable to damage of the liver was wanting in case 1, microscopically a rapidly degenerative lesion was seen, which may have developed in a few hours or in a few days at most. It would appear from this case that intense bile staining of the hepatic parenchyma, so frequently observed in yellow atrophy of the liver, may be the result of abnormal function and excretion of this pigment by the cells that remain rather than of a biliary obstruction coincident with the injury, for it is absent in the acute stage.

It is to be noted in these three cases that the gross and the microscopic appearance of the liver were characteristic, and did not suggest that acute yellow atrophy is an end-result of an extensive central necrosis like that which may occur following intoxication with such chemical poisons as chloroform or with streptococcic and other infections. The lesions are essentially focal in character, do not affect the hepatic lobules uniformly and are relatively large; consequently, in all stages the morbid anatomy of the liver is that of complete destruction of entire areas of parenchyma with an escape of the larger or smaller areas, which in time become hyperplastic. The process differs in this respect from the effect of known toxic agents circulating in the blood and suggests the presence of some unknown local disturbance in the liver, irregular in its distribution, as an essential or contributing factor. In the subacute, chronic and healed stages, the liver grossly appears coarsely lobular and irregular in the extent of lobulation. If the lesion is healed, it is necessary to determine histologically that entire lobules of hepatic parenchyma have been destroyed in order to make a diagnosis of the condition. As Mallory pointed out, one must find the skeleton of former lobules as outlined by a persistence of bile ducts with a collapsed vascular stroma between.

It does not seem justifiable, however, to diagnose the condition of a healed liver as "toxic cirrhosis," if by that term is meant the end-result of a central necrosis of the type so commonly seen as a terminal event after certain severe infections or after chemical poisoning. Rather, acute yellow atrophy should be considered as a distinct disease with characteristic irregularity in the extent of its lesions, and of unknown etiology; it is not duplicated by any known intoxication. Consequently, we favor the continued use of the terms acute, subacute and chronic stages, as emphasized by Strumpell, Seyfarth and Brütt, and the term a healed stage of yellow atrophy. Although these designations are imperfect, we believe they should be retained in order to preserve the identity of this peculiar disease, pathologically as well as clinically, until it can be given a more precise definition on etiologic grounds.

SUMMARY

1. Cases illustrative of an acute, a subacute and a healed yellow atrophy of the liver are presented.

2. Recovery from acute yellow atrophy is probably more frequent than is generally believed.

3. Different stages of the disease have been accurately recognized pathologically, namely, acute, subacute, chronic and healed stages.

4. In the healed stage, the liver is grossly and irregularly lobulated. The hepatic parenchyma is represented by irregular masses of hyperplastic liver cells, which are separated by a vascular, collapsed stroma in which the skeleton of previous lobules persist to a greater or less degree. From this histologic picture the diagnosis may be made.

5. As the initial lesion of acute yellow atrophy differs in distribution and in extent, if not in kind, from that of the ordinary toxic central necrosis, and as we are yet ignorant of the etiology, it is believed that the term "healed yellow atrophy of the liver" is preferable to the term "toxic cirrhosis" as applied to the condition of the liver which is healed.

POLLINOSIS

CONSTITUTIONAL AND LOCAL FACTORS

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The wide prevalence of hay-fever alone would justify presentation of any new concept offering possibilities of increased therapeutic efficiency. Conservative statisticians estimate that fully 1 per cent of the population of the United States is afflicted with hay-fever.[1] The malady is sufficiently incapacitating, but when it is considered that 65 per cent of all persons with hay-fever finally become asthmatic,[1] the need for further developments in treatment becomes even more obvious. Interest in these sufferers is not alone humanitarian, for the economic loss to the victim is often great. Those who do not have hay-fever know well the debilitating effect of an ordinary acute coryza, and realize the struggle of those who must work at full efficiency while semiprostrated for weeks or months with an unrelenting rhinitis. Even the welcome asylum of the hay-fever resort, usually located in a heavily timbered area in which weeds were few, has in great measure lost its power to give relief, increasing popularity having resulted in the building of large hotels, the clearing and cultivation of acreage and the consequent proliferation of weeds.

Hay-fever, recognized in the history of medicine for nearly 400 years, since its description in 1565 by Botallus of Pavia, does not fail to justify its name as much as some have asserted. It is true that the major portion of cases in the United States occur some time after the period of timothy pollination and are attributable to the pollination of ragweed; but hay-fever was so designated and studied in England long before the American literature contained extended references, and in England even now the disease appears to be more prevalent in May and June, being well on the wane in early August.[2] Hay-fever and rose-fever, however, are descriptive titles which are too often incorrect both in their etiologic insinuations and in their intimation of a febrile reaction. A truer descriptive title should carry with it either the implication of an allergic state in the patient or a more accurate designation of the provocative cause. Since pollens of one kind or another are almost invariably the immediate agent producing seasonal rhinallergic reactions, we propose to adopt the term "pollinosis." It is true that

1. Balyeat, R. M.: Hay-Fever and Asthma, Philadelphia, F. A. Davis Company, 1926, p. 12.

2. Vaughan, Victor C.: Epidemiology and Public Health, St. Louis, C. V. Mosby Company, **1**:65, 1922.

allergens other than pollens, such as orris root, animal dander or dust, will produce the symptoms of vasomotor rhinitis even with seasonal recurrences, but if the statement that 95 per cent of all such cases are attributable to pollens is correct, the term "pollinosis" will fit the case as satisfactorily as do the designations of the majority of known diseases.

The functional pathology of pollinosis can be satisfactorily discussed only in conjunction with the pathology of allergic reactions in general. Only those pathologic observations that have a direct bearing on certain concepts will be presented in this article. Anaphylactic shock is a constitutional reaction, its site apparently being intracellular. The outstanding recognizable functional alteration consists of increased spasticity of smooth muscle.

General anaphylactic reactions present different clinical pictures in different experimental animals. In the guinea-pig, after a preliminary mild stage in which there is evidence of nasal irritation with sneezing and scratching of the nose, the symptoms become chiefly respiratory, comparable to those observed in a human being with asthma, and at necropsy the outstanding feature is pronounced spasm of the smooth muscles of the bronchioles.

In rabbits that have died from anaphylactic shock, distention of the lungs is not observed, but the evidence points to a pronounced tonic spasm of the muscular coat of the pulmonary arterioles. There may possibly be a similar increased tonicity in the systemic circulation.

In dogs the outstanding feature is a pronounced fall in blood pressure, apparently due to some action on the neuromuscular nerve endings. With this, but not dependent on it, there is an increased flow of lymph and a severe local reaction in the intestines. This amounts practically to an acute enteritis with edema and petechial hemorrhages in the mucous membrane of the gut, the lumen of which is often filled with mucus mixed with blood. Manwaring [3] has found that the liver in dogs is a most important organ in the production of anaphylaxis. With the liver out of the circulation, anaphylactic shock does not occur in dogs. Weil [4] suggests that most of the circulatory disturbance in the dog may be attributed to obstruction in the portal circulation.

He suggests that the differing symptoms in these three types of laboratory animals are due primarily to differences in quantitative distribution of smooth muscle. He finds there is an astonishing development of the bronchial musculature in normal guinea-pigs, while the pulmonary arteries of rabbits present a remarkable degree of muscular development. The walls of the hepatic veins of dogs differ from those of the other animals in showing again a high muscular development. It

3. Manwaring and Crowe: J. Immunol. **2**:517, 1917.

4. Weil, Richard, quoted by Zinsser: Infection and Resistance, New York, The Macmillan Company, 1923, p. 437.

is true, particularly among dogs and rabbits, that not all animals selected for experiments respond equally well to induced anaphylaxis. It seems possible that this variability may depend, in part at least, on the varied distribution of these muscle preponderances. This suggests attractive speculation as to why some allergic persons develop hay-fever or asthma, others headaches or the symptoms of an acute gastro-enteritis, while others show predominantly dermal manifestations.

That anaphylaxis may be manifested only as a local reaction is demonstrated by the classic experiments of Arthus,[5] who, while working on rabbits, found that repeated subcutaneous injections eventually gave rise to edema, sterile abscesses and even gangrene at the sites of inoculation.

Coca [6] maintains that experimental anaphylaxis and clinical allergy, while presenting features of greatest similarity, cannot be considered as strictly identical, because in the latter it has not been definitely proved that there is an antigen-antibody reaction. Van Leeuwen [7] presents evidence that clinical allergy actually is an antigen-antibody reaction. Kolmer [8] believes that Coca's insistence on the demonstration, by passive transfer, of antibodies in the serum of a sensitive person is too rigid, since antibodies may be developed in a sensitized animal, including man, without being successfully transferred by injecting the serum into another animal. He doubts the justification for making a division on the basis of the ability to demonstrate antibody production. The technic for discovering antibodies is too imperfect. It is also possible that antibodies may be present in cells when their presence in the blood cannot be demonstrated.

The symptoms of pollinosis result from the contact of a sensitive person with a specific allergen, usually a pollen protein. The reaction may be local, limited to the upper part of the respiratory tract, or it may become generalized, with the symptoms of asthma predominating.

It seems reasonable to suppose that the reaction in the nasal mucosa may be a purely local sensitization reaction, but it must be borne in mind that nearly all of these patients show evidences of a generalized sensitization in the positive cutaneous reaction at a point far removed from the nose. All such cases of pollinosis should be considered systemic and the general or systemic point of view should determine the method of treatment. But is pollinosis purely systemic, or does local sensitization also play a part? If the pollen protein were to gain access to the body

5. Arthus: Compt. rend. Soc. de biol. **48**:817, 1903.

6. Coca: Tice's Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., **1**:110, 1920.

7. Van Leeuwen, W.: Allergic Diseases, Philadelphia, J. B. Lippincott Company, 1925.

8. Kolmer: Infection, Immunity and Biologic Therapy, Philadelphia, W. B. Saunders Company, 1924, p. 598.

through some other portal, such as the skin, the stomach or the colon, would the symptoms still be those of "hay-fever," indicating that the reaction is entirely general but with predominant symptoms in the nasal mucosa? There is no doubt that nasal symptoms are a part of a generalized reaction. I have already referred to the nasal irritation in anaphylactic guinea-pigs. Patients not infrequently experience sneezing during preseasonal desensitization when the hypodermic dose approaches the limit of tolerance. Bernton has mentioned a most interesting case of a man sensitive to dust, who, shortly after the hypodermic injection of dust extract, the nature of which he did not suspect, complained of an uneasy sensation in the nose, saying that it felt as though he were inhaling dust.

While sneezing clearly appears to be a factor of systemic reaction, there is also evidence that local sensitization plays a part.

I have elaborated my method of treatment on the basis of the following hypotheses. While the treatment is in general orthodox, I present an additional conception on the systemic side which has not received the consideration I believe it deserves.

1. Pollinosis is primarily a constitutional disease in which the patient's tissues are generally sensitive to the particular pollen that causes the symptoms. Nasal localization is sometimes a resultant of the systemic reaction. To obtain the best results, the constitutional factor must be taken into consideration.

2. The localization of the reaction in the nose may be due in part to a specific sensitization of the tissues of the nasal mucosa.

3. The factor deciding nasal localization may equally well be nonspecific, such as mechanical irritation in the nose. Such a nonspecific provocative cause usually would not, however, produce the symptoms if a specific constitutional predisposition did not exist at the same time.

4. In a person with pollinosis there may be a coexistent sensitization to some protein which would not cause the symptoms of "hay-fever," but the reaction to which, superimposed on the pollen reaction, enhances the manifestations of the latter.

The first postulate scarcely requires further elaboration; it should be granted by all. The second proposition appears equally logical. The Arthus phenomenon mentioned demonstrates experimentally the possibility of a local tissue sensitization reaction. If one can obtain a positive skin test on the back or arm of a person with pollinosis, it is but logical to assume that a similar local sensitization reaction, strictly specific, will occur in the nasal mucosa. The positive ophthalmic reaction is a similar example. Indeed, this conception was the rationale of the preseasonal desensitization with nasal sprays containing increasing concentrations of the specific pollen recommended a few years ago by

McKenzie.[9] This treatment alone, however, does not take into consideration the systemic desensitization. I used it through one season, directing the patient to apply the doses several times daily with an atomizer; at the same time, I treated him for the systemic condition by the usual preseasonal hypodermic inoculation. The results were good.

Cooke, Duke and others have reported cases of typical seasonal pollinosis in which the results of the sensitization tests with pollens were negative. I record three such cases. Among 200 cases, Kern [10] reports 4 typical seasonal cases in which the patients gave negative skin reactions to pollens. Two of these received conjunctival tests, one being weakly positive thereto. Three were treated with pollen extracts appropriate to the season, with good results. He believes that these are true cases of pollinosis with local sensitization only. It would have been of interest to know whether nasal instillations of pollen extract would have produced a reaction; also whether the skin tests did or did not become positive after subcutaneous desensitization.

On the other hand, the recent work of Bernton,[11] in which he shows that one may be sensitive to only one of the constituent proteins of the pollen, may account for these negative reactions. He found that just as one may give a negative reaction to the whole wheat protein and a positive reaction to one of the constituent wheat proteins, so one may give a negative reaction to the usual pollen protein, but a strongly positive response to one of its fractionations.

The third postulate—that nonspecific irritation increases the local symptoms—in my opinion, accounts for the benefit often attributed to and actually following nonspecific therapy. Whoever has seen a spiculated pollen spore under the microscope requires little imagination to understand that the pollen itself, besides its specific antigenic properties, is an actual mechanical irritant of decided significance. Auer [12] has convincingly shown experimentally how a mechanical irritant will determine localization of the reaction in a sensitized animal or person. Xylol applied to the ears of nonsensitized rabbits did not produce a great degree of inflammation. On the other hand, when xylol was applied to sensitized animals which were then given otherwise ineffective doses of antigen, local necrosis occurred. He concluded that the inflammatory action of xylol caused accumulation of effective amounts of antigen in the locality affected.

The following illustrative cases will bring out some of these points more clearly and will preface a more extended discussion of the fourth postulate.

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9. MacKenzie, G. M.: Desensitization of Hay-Fever Patients by Specific Local Applications, J. A. M. A. **68**:787 (March 18) 1922.
10. Kern: Ann. Clin. Med. **5**:371, 1926.
11. Bernton, Harry S.: South, M. J. **20**:257 (April) 1927.
12. Auer: Proc. Soc. Exper. Biol. & Med. **17**:93, 1919.

ILLUSTRATIVE CASES

CASE 1.—The patient had had fall hay-fever for several years, which came on any time between the 1st and the 15th of August. She had been given courses of ragweed desensitization, never with satisfactory results. On being tested, she gave a negative reaction to ragweed, a three plus reaction to sunflowers and two plus reaction to golden rod. Following daily hypodermic desensitization with golden rod for three weeks prior to August 1, the patient experienced practically 100 per cent relief throughout the 1926 season.

Antecedent failure was due to the physician's failure to realize that sensitization is specific and may be due to some pollen other than ragweed. If a careful history had been taken, this would have been suspected, since ragweed pollinosis never begins before the 15th and rarely before the 20th of August.

CASE 2.—The patient had early spring and fall hay-fever and was strongly sensitive to roses, orchard grass, June grass and sunflowers and mildly sensitive to daisies and ragweed. There was a negative reaction to timothy. Some manufacturers of pollen extract advise that since 90 per cent of spring and summer pollinosis is due to timothy and 90 per cent of the fall variety to ragweed, these two pollens may be used with the expectation of 90 per cent of relief.

This is one of the many examples of the cases in which desensitization with timothy would have been a complete failure.

CASE 3.—A woman who had vasomotor rhinitis of four weeks' duration reacted clearly to the pollen, but not to the grain, of corn. At first she denied eating corn, but later recalled that she had been eating hominy daily during the period of sneezing and not previously. She lived in the city, and the possibility of local pollen effect seemed remote. She omitted corn and hominy from the diet, and was promptly relieved. I have had two patients who were sensitive to the pollen but not to the protein of corn, and who developed attacks of sneezing after eating food containing corn. In these cases there was a reaction due to a constitutional sensitization; the portal of entry was the stomach, but the constitutional reaction was manifested in the nose.

This is an example of pollinosis in which the local symptoms are not due to local reaction. The observation that the sensitization was due to an article which customarily causes nasal symptoms on local contact is of interest.

While probably most cases of perennial vasomotor rhinitis accompanied by sneezing in and out of season are dependent on local contact, as with powders or soaps containing orris root, horse dander, the dust from feathers and rabbit hair, house dust, etc., I have had a series in which the sneezing followed the ingestion of food to which the patient was sensitive. This is not infrequent in the experience of others, but differs from the last two cases described in that these patients were sensitive by test to the pollen but not to the food, and yet had symptoms on contact with the latter.

CASE 4.—The patient with severe rhinorrhea occurring during the ragweed season, who was found strongly sensitive to the hair of dogs and rabbits, less so to feathers, dahlias, orchard grass and dandelions, and with negative reactions to foods, did not improve on avoidance of these causes or on local palliative treatment of the nose. Roentgen-ray examination, however, showed evidence of a maxillary sinusitis, and drainage of the sinus gave prompt relief.

Here sensitization may not have played a part, but the symptoms were those of pollinosis; and headache, local pain or tenderness, fever or leuko-

cytosis were not present, as one would expect in sinusitis. A local mechanical factor produced allergic symptoms in a person shown by positive skin tests to be in an allergic state.

CASE 5.—The patient, whose only symptom was sneezing, did not give any positive food, pollen or epidermal reactions, and his symptom was promptly relieved by the extraction of an abscessed upper canine tooth.

This case and case 4 show that while attention is being directed to allergy, the possibility of a purely local pathologic change must not be overlooked. I have no doubt that those cases of asthma in which the rhinologists give relief by argyrol tamponage of the ethmoids are associated with local infection.

While the allergist probably fails too frequently to recognize such local pathologic changes, his error has not the same serious significance as that of the rhinologist who submits the patient to unnecessary intranasal operation while the cause is constitutional. A patient with a typical vasomotor rhinitis of eight years' duration had had the polyps removed, the ethmoids operated on, and submucous resection, all without benefit and was then promptly relieved after he avoided the use of orris root, beans, peas, garlic, sweet potato and wheat.

CASE 6.—The patient gave mild reactions to the proteins of chicken and of chicken feathers. By avoiding these irritating proteins, he was relieved of a mild condition of asthma, which consisted chiefly of tightness in the chest without outspoken attacks. Although not sensitive to ragweed or other pollens, and although not manifesting the symptoms of pollinosis, he is ill at ease during the pollen season, more so when in the country than in the city and particularly when in the neighborhood of ragweed.

In this case it seems reasonable to conclude that the purely mechanical irritation from pollen in an otherwise mildly allergic person produces the symptoms.

CASE 7.—The patient had a typical ragweed hay-fever of five years' duration and a history of attacks of urticaria of fifteen years' duration. Attempts at ragweed desensitization during the preceding four years had been unsuccessful. The patient was first seen during the hay-fever season; she was suffering with severe hay-fever which had not been mitigated by preseasonal desensitization. She was clearly sensitive to daisies, sunflowers, roses and ragweed. She was tested with various foods and reacted to the proteins of egg, wheat, carrot and pepper. After omission of these foods from the diet, the hay-fever was promptly relieved.

I shall now discuss the fourth postulate. I have recorded elsewhere [13] my theory of an allergic equilibrium or balanced allergic state. Briefly, the hypothesis is as follows: A person may be sensitive to some food protein, such as a food with which he comes in frequent, even daily, contact, and yet remain free from symptoms. Peshkin and Rost [14] and Rackemann [15] have found that about 10 per cent of children without symptoms of allergy are sensitive to one protein or another. They are

13. Vaughan, W. T.: South. M. J. **27**:749, 1924; Virginia M. Monthly **51**:472, 1924.

14. Peshkin, M. M., and Rost, W. L.: Incidence of Protein Sensitization in Normal Child, Am. J. Dis. Child. **23**:51 (Jan.) 1922.

15. Rackemann: Am. J. M. Sc. **163**:87, 1922.

allergic but are in equilibrium. The tissues are able to handle a given quantum of the allergen without upsetting the allergic balance. Perhaps desensitization from frequent ingestion of small amounts is a factor. An overdose of the allergen, however, will upset the equilibrium with consequent precipitation of symptoms.

One may be sensitive to two proteins, maintaining allergic balance while the contact is with one only, but developing symptoms on exposure to both. It may be unnecessary to remove both for relief, the equilibrium being reestablished on the avoidance of one. In the case just described, the patient was sensitive to certain foods, the strongest reaction being to egg. She had eaten wheat and eggs practically daily in the past with no symptoms other than an occasional urticaria. She was allergic but practically in allergic equilibrium. When exposed to ragweed pollen, she developed the typical symptoms of pollinosis. Desensitization gave little or no relief, but another therapeutic procedure remained possible. The food proteins were eliminated, the additional tax on the system was relieved, and the patient returned to a balanced allergic state in spite of continued contact with ragweed proteins.

CASE 8.—The patient had suffered from ragweed pollinosis for years. There was an accompanying ragweed asthma, but no asthma at other times during the year. He was strongly sensitive to ragweed and mildly so to the hair of rabbits and dogs, chicken feathers and nine food proteins. He was relieved from hay-fever, but not from asthma, by coseasonal desensitization. There was prompt relief after avoidance of the food and other proteins to which he was sensitive. Through the year he had been able to sleep on feather pillows and felt mattress and to eat the food to which he was sensitive without disturbance of the allergic equilibrium.

My co-workers and I have had several other patients with pollinosis who were not relieved or who were only partially relieved by pollen desensitization, and who have subsequently been further relieved or cured for the season by avoidance of other proteins, usually in the food. Therefore, when a patient with pollinosis does not respond satisfactorily to treatment, he is tested as a matter of routine, with the food and epidermal proteins.

In these cases both factors at work are specifically allergenic. It is my belief that one of the factors may be nonspecific. A person sensitive to a protein but remaining in allergic equilibrium may manifest symptoms after the action of some mechanical provocative cause. This is more often seen in allergic states other than pollinosis. The experimental work of Auer mentioned in the foregoing might be cited as an example. Dermatographia produced after mechanical irritation in an allergic person is an example. A person sensitive to a food which he is eating daily may remain in balance until the mechanical irritation of a tight collar produces a local eczema.

CASE 9.—The patient complained of a seasonal hay-fever which lasted from March until the first frost. She gave negative reactions to all of the available pollen proteins. In order to be certain, these tests were all repeated, and the results again were negative. She gave borderline reactions to several foods, and after eliminating them from the diet, she experienced from 50 to 75 per cent improvement. She was not given local nasal treatment while on the diet.

In this case the allergic balance was evidently overthrown by the mechanical irritation of the pollens in the inspired air. This case recalls those described by Kern. It would have been of interest to know whether his negative pollen reactors were sensitive to other proteins, such as food proteins.

CASE 10.—The results in this case may be explained in the same manner. A woman had perennial vasomotor rhinitis which, however, was decidedly worse during the ragweed season. There was a negative reaction to all pollens, a three plus reaction to the feathers of geese and ducks and to the hair of rabbits, a two plus reaction to oats and rice, and a one plus reaction to lettuce, squash and the hair of dogs. Treatment consisted of avoidance of the irritants. Prompt relief was experienced, and the patient has since gone through two ragweed seasons without symptoms.

COMMENT

I have attempted to show that there are often two, three or even more causative factors or agents which must be taken into consideration in the treatment of patients who have simple pollinosis. The disease is constitutional with local manisfestations. Often two factors may be grouped, one as predisposing and the other as exciting or provocative. Usually the predisposing factor is specific, as exemplified in my discussion of allergic equilibrium or the balanced allergic state. The provocative cause may be specific, allergenic, or nonspecific, nonallergenic. The exciting cause may exert its action either constitutionally or locally. Constipation, focal infection, endocrine disturbance, exhaustion, possibly calcium deficiency and the like may play nonspecific parts. For the greatest success, however, the basis of treatment must be a conception that pollinosis is a constitutional allergic disease.

There are other details in a consideration of the treatment, but space does not permit discussion of them. One of particular interest is nonspecific desensitization, as with peptone. Suffice it to say that I have had more poor results than good ones with peptone, but sufficient good results to justify trial when other methods have failed. I do not know precisely how nonspecific desensitization reduces tissue reactivity. Wells speaks of tissue inactivation when, through exhaustion, drug action or other injury, the sensitized cells cannot respond to the antigen-antibody reaction.

The remarkable fact is that early in the development of the present system of pollen desensitization such good results were usually obtained. Short lived saline extracts have now been replaced by more permanently potent glycerin and alcohol extracts. Formerly coseasonal treatment was avoided as dangerous. Since good results from daily coseasonal injec-

tions were first reported in 1923,[16] this method has been generally adopted in appropriate cases. Indeed, Duke [17] has recommended daily inoculations over a shorter time in his preseasonal work, and I am able to say that in the 1926 season I obtained far superior results with the Duke method than with any other preseasonal system that I have employed.

Phillips [18] reports good success with daily coseasonal inoculations. He appears to have obtained excellent results from daily intradermal injections, a method which would appear to have decided advantages and few disadvantages.

The investigations of Bernton already referred to represent another advance in the work with the pollen protein itself and, like the improvements just mentioned, will promote greater success in specific pollen desensitization.

In spite of these forward steps, however, cases remain in which the patients do not respond satisfactorily. In these the application of the concepts brought forward in this paper will further increase the percentage of good results.

A closer liaison between the allergist and the rhinologist is desirable. Local pathologic change serves as a nonspecific predisposing factor and helps to disturb allergic equilibrium. The rhinologist should cooperate to remedy these defects, but he should complete his work out of season. Aside from making sedative applications, he cannot do any good during the attack, and reconstruction work will be productive of harm. It is better to remove polyps, but this should be attended to before the symptoms commence. The patient with pollinosis should consult a rhinologist preseasonally for local renovation at the same time that he consults an allergist for preseasonal desensitization.

Success in the treatment of this disease depends on many factors. Among the more important are the following:

1. Recognition of the specific cause.

2. Ample specific therapy with a proved potent antigen, either preseasonally, or coseasonally, or both.

3. Prevalence of pollen. Too great a dose of antigen will overcome the the most efficient preliminary desensitization. Conversely, the good results attributed to specific therapy are sometimes due in part to a low prevalence of pollen. Two workers in different sections using identical therapy may observe radically different results due, not to the method, but to differing prevalence of pollen.

4. Weather conditions. Sun, wind and rain determine the abundance of seasonal vegetation and the distance to which the pollen will be carried.

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16. Vaughan, W. T.: Specific Treatment of Hay-Fever During the Attack, J. A. M. A. **80**:245 (Jan. 27) 1923.

17. Duke: Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy, St. Louis, C. V. Mosby Company, 1925.

18. Phillips: Relief of Hay-Fever by Intradermal Injections of Pollen Extract, J. A. M. A. **86**:182 (Jan. 16) 1926.

5. The absence of too great physical alterations in the upper part of the respiratory tract.

6. Avoidance of mechanical irritation such as from dust.

7. Recognition and removal of other constitutional factors, either allergenic or nonallergenic, which through their presence diminish functional efficiency and help disturb the allergic balance or equilibrium.

8. Cooperation of the patient. Treatment properly applied is not altogether pleasant. It is time-consuming and exacting. Other considerations being equal, the more cooperative the patient, the greater will be the anticipation of good results.

CORRECTION

In the article by Dr. Albert H. Rowe, entitled "House Dust in the Etiology of Bronchial Asthma and of Hay-Fever" (ARCH. INT. MED. **39**:498 [April] 1927), an error occurred in the last paragraph on page 501: 5 per cent salt solution was used, instead of 0.5 per cent solution, as there stated.

Book Reviews

SYPHILIS UND INNERE MEDIZIN. VON HERMANN SCHLESINGER. II Teil: Die Syphilis der Baucheingeweide. Price, 19.50 marks. Pp. 289. Berlin: Julius Springer.

The author says in his preface that this work deals with diseases that for the most part are well known, even though there is still lively discussion concerning many of them. He also says that he approaches the subject as a clinician, as an "alter Krankenhausarzt." His aim is to present facts rather than theories. He admits that he is of a skeptical turn of mind and does not accept uncritically all that has been written about visceral syphilis. One sees that he has a knowledge of chemical and other laboratory aids to the diagnosis and understanding of this topic; but it is also clear that in the study of a case Schlesinger does not depend entirely on the van den Bergh test, or the Wassermann reaction, the sedimentation of the blood or on the roentgen ray. There is old fashioned reliance on the history, subjective symptoms, palpation and percussion. It is refreshing to read how syphilis of the liver is diagnosed largely by such symptoms as pain, fever, the size and shape of the organ and by the therapeutic test. Without disregarding the examination of the blood, he tells us how misleading the Wassermann test may be. Some have contended that in this disease there are characteristic numerical changes in the leukocytes. Schlesinger has frequently seen a relative lymphocytosis, but he concludes that "in syphilis of the liver no definite blood formula exists and — with the exception of the serologic examination — the blood findings have no definite diagnostic or prognostic significance." There are scores of helpful diagnostic hints such as only an experienced observant practitioner could give. Thus he says that bloody stools should not lead one too readily to believe that there are esophageal varices or ulcerative processes due to the disease. They may often be due to a mercurial enteritis, the result of over-vigorous medication.

And so all through the subjects of syphilis of the liver, stomach, spleen, kidney, pancreas and bowel, the practical, well tried, clinical features are stressed rather than the newer and theoretical. It is not to be concluded, however, that theory and pathogenesis are overlooked. These are given fair consideration. As a good example may be cited his argument and conclusions concerning arsphenamine icterus. Syphilis and nutritional disturbances furnish the groundwork for the icterus. The drug, however, damages the liver parenchyma and leads to the icterus and liver atrophy, (p. 80).

The book is easily read. There is a good bibliography, especially of German literature. To one who wishes help in practical clinical work in syphilis of the abdominal organs, the book may be warmly recommended.

THE CONQUEST OF DISEASE. By THOMAS B. RICE, M.D., Assistant Professor of Sanitary Science, Indiana University School of Medicine. Cloth. Price, $4. Pp. 363, illustrated. New York: The Macmillan Company, 1927.

This interesting book was written primarily for the laity and general students, with three main purposes in view: (1) to set forth the most recent scientific information concerning the transmissible diseases to the end that these diseases may be controlled or perhaps ultimately eradicated, (2) to make the subject interesting, if possible, to the general reader, and (3) to

emphasize the great advances that have been made through scientific methods by comparing the past with the present.

One is impressed with the accuracy and fairness of the contents, as well as with their clarity and simplicity; there is little opportunity for disagreement, and the use of highly technical terms is avoided. Much interest is added by short historical accounts of each disease and by a review of many of the superstitions which arose from ignorance, misunderstanding and religious fanaticism.

Part one consists of a general survey. Part two is devoted to a detailed study of each disease, grouped according to the manner of transmission. The final chapters are devoted to a consideration of the means of control and explain the rationale of public health administration, sanitation, quarantine regulations, vital statistics, and registration of births and deaths. There are no misstatements of fact, and the author's sincerity and humanitarianism should make a strong appeal to every intelligent reader. Information of this character, presented in such masterly fashion, cannot fail to advance the cause of scientific medicine.

TRAITÉ DE PHYSIOLOGIC, NORMALE ET PATHOLOGENIQUE. Published under the editorship of Drs. G. H. Roger and L. Binet, Professors of Physiology in the Faculty of Medicine, University of Paris. Volume 7. Blood Lymph and Immunity. Price, 65 francs. Pp. 502, with illustrations. Paris: Mason et Cie, 1926.

This volume on normal and pathologic physiology deals with blood, lymph and immunity. It is a composite effort of eleven authors, with chapters on the morphology of the blood, hemoglobin and its derivatives, respiratory albuminoids of invertebrates, blood plates, bone marrow, blood coagulation, hemorrhage, blood transfusion, the lacunar system (including edema, dehydration, etc.), lymph and lymph products, lymph glands, immunity (this chapter by Bordet) and anaphylaxis. Each chapter has limited references to the literature. The book as a whole is weakened by the absence of an index at the end, so that one has to hunt for the matter through the schematic table of chapters. The chapter by Bordet on immunity is particularly excellent. It seems strange, however, that in such an ambitious monograph on the physiology and pathology of blood and lymph with chapters on hemorrhage and edema, there should not be a chapter on the various types of anemia. One is also struck by the fact that in the chapter on the physiology and pathology of the blood plates, reference is not made to the recent work of Howell on the significance of the blood plates in hemophilia. The book as a whole, however, is readable, lucid, reasonably comprehensive and up to date.

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